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THE CYTOLOGIC METHOD AS AN AID IN THE DIAGNOSIS OF GASTRIC CARCINOMA

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CARCINOMA of the stomach is encountered more frequently than is any other malignant lesion today. Surgical extirpation has been the only effective means of treatment but the disease is so insidious in its onset that extirpation is rarely possible. Pack and Livingston in 1940 made the statement that, "at no time in surgical history and at no point in the world have the definitive cures of gastric cancer ever exceeded 5 per cent of the total number of cases with this disease." In 1942 Walters, Gray, and Priestley reported 6.2 per cent 5 year cures in a series of 10,890 cases. Abrahamson and Hinton in a recent paper state that only 5 per cent of their 139 cases of gastric cancer could be considered candidates for cure. Welch and Allen at the Massachusetts General Hospital have found 6.5 per cent of 375 patients surviving at the end of 5 years. It is obvious that although gastric surgery has grown steadily more radical and less hazardous, the rate of cure remains low.

Cancer of the stomach is usually moderately advanced before it produces any symptoms at all. If any significant increase in the rate of operability with expectation of cure is to be achieved, we must devise some means of detecting the disease in its presymptomatic state. One such effort was reported in 1944 by St. John, Swenson, and Harvey. Using a technique of rapid fluoroscopic scanning of the stomach, they discovered three malignant gastric tumors in 2,413 individuals over the age of 50 years. None had digestive symptoms of clinical note. Five other patients were explored and benign ulcers were found.

We are presenting in this paper a preliminary report on our experience with another diagnostic measure which may be of value in discovering early gastric carcinoma—cytologic examination of gastric fluid for the presence of malignant cells.

The cytologic method in the diagnosis of carcinoma was introduced by Papanicolaou in 1928 (7). The method depends on the observation that most malignant growths desquamate cells which can be identified after suitable fixation and staining. The original report dealt with uterine carcinoma and has been confirmed by many investigators (2,5). It was an obvious step to apply the cytologic method to other body fluids. In 1937 Dudgeon and Wrigley reported 66 per cent accuracy in the diagnosis of cancer of the lung by examination of the sputum. Wandall in a series of 100 pulmonary carcinomas found malignant cells in the sputum of 86 per cent. Papanicolaou in 1945 (9) mentions 9 patients in whom the gastric secretions obtained by aspiration were studied. Two had gastric carcinoma and malignant cells were seen in the gastric fluid.

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In the past year at the Vincent Memorial Laboratory gastric aspirations from 50 patients suspected of cancer of the stomach were studied by the cytologic technique.

METHOD

1. A fasting specimen of gastric secretion is obtained by aspiration. In this series gastric aspirations were used rather than gastric washings. It is of the utmost importance that the specimen be sent to the laboratory *immediately*, since if there is more than half an hour's delay the cells are digested and no distinct cellular characteristics can be identified.

2. The specimen is centrifuged immediately, the sediment spread on a glass slide and placed at once in a fixative of equal parts ethyl ether and 95 per cent alcohol.

3. After fixation for at least 15 minutes, the slides are stained by Papanicolaou's method (8).

CYTOLOGY OF GASTRIC SECRETION

Normal cells. Most of the cells normally encountered in the gastric secretion originate in the squamous mucous membrane of the upper gastrointestinal and pulmonary tract. These are large epithelial cells with a clear cytoplasm and a small, vesicular nucleus. Often epithelial cells from the gastric mucosa are seen. These appear as cuboidal or columnar cells with an eccentric nucleus which is small and vesicular. Occasionally these columnar cells are flattened and then they appear as great sheets of cells with nuclei of even size and single nucleoli. If the cells are well preserved, cellular borders are distinct. If the cell group has undergone some degeneration, the cytoplasmic outline may disappear, although the nuclei remain sharply defined.

Erythrocytes, neutrophils, lymphocytes, and histiocytes are usually seen. Bacteria are common and cocci in groups of four are noted fairly frequently.

Malignant cells. The malignant cells seen in gastric secretion often appear in groups. They have nuclei which are hyperchromatic and usually contain prominent nucleoli. There are no sharp cellular borders. Often the cytoplasm shows vacuolization, a characteristic of adenocarcinoma. There are occasional single cells which can be identified as malignant. They have large, hyperchromatic nuclei and an inadequate amount of cytoplasm.

RESULTS

In this series of 50 cases, 24 had carcinoma of the stomach. Cancer cells were seen in the gastric fluid of 15. The error in the positive cases is 37.5 per cent.

All 24 of these patients were explored. Seven of the lesions were resectable and 5 of these had previously shown malignant cells in the gastric secretion. One of the two failures in this small group was a scirrhous carcinoma of the wall of the stomach without ulceration of the mucosa. Such a tumor could not be expected to shed cells into the gastric lumen.

In 26 cases no evidence of cancer was shown. Fourteen patients were explored. Twelve were proved to have benign gastric ulcers; 1 had a neurofibroma of the stomach; and 1, a benign duodenal ulcer. The gastric cytology was correctly diagnosed as negative in 25 instances. One positive cytological report was rendered in a case later proved to have a benign gastric ulcer. The error in the benign cases is 3.8 per cent.

Below are abstracted two cases which illustrate the value of the method:

P.R., M.G.H., No. 521265. This 50 year old man entered the hospital with the complaint of crampy, postprandial, midepigastric pain of 14 months' duration. He had obtained relief for the first 8 months on a liberal low fat, bland diet and antiacid medication. The symptoms had then recurred. He had lost 5 pounds in weight over the course of a year but had noted no blood in his stools. *Gastric analysis* showed no free acid in the fasting specimen, there were 27.0 units in the first sample after histamine. *Gastrointestinal x-ray examination* showed marked spasm of the antrum, probably due to a benign ulcer in the middle third of the lesser curvature. *Cytologic examination of the gastric fluid* was positive. A subtotal gastrectomy was performed. *Pathological examination* of the specimen showed a gastric ulcer with multiple foci of carcinoma *in situ*. Further sections revealed one area of invasive growth with penetration beneath the muscularis mucosa and involvement of nerve and nerve sheaths. The lymph nodes were negative.

H.S., M.G.H., No. 521291. This 67 year old man entered the hospital with the complaint of intermittent, severe, upper abdominal and substernal pain occurring 1 to 2 hours after eating. He had not vomited and had noted no blood in his stools. He had

lost 20 pounds in weight. *Gastrointestinal x-ray examination* showed an ulcerative lesion (2.5 by 1.5 cm.) in the upper stomach which could be either malignant or benign. *Cytologic examination of the gastric fluid* was positive. A transthoracic total gastrectomy was performed. *Pathological examination* of the specimen showed a benign gastric ulcer. The lymph nodes were negative. These sections were reviewed and one area of preinvasive carcinoma was found at the periphery of the ulcer.

DISCUSSION

Any approach which promises to bring cancer of the stomach to operation sooner than in the past merits attention. Mass radiography is one avenue of attack. We feel that the cytologic method may also be of great value in this problem. Although 9 of the 24 cases of carcinoma in this series were erroneously called negative on cytologic examination, only 2 of the 7 resectable cases were missed and 2 extremely early cases were both diagnosed correctly. The observation that preinvasive carcinoma sheds cells which can be recognized as malignant is of fundamental significance. This fact has already been noted in carcinoma of the cervix (4). The increased accuracy of the cytologic method in early lesions may be due to the presence of active, healthy, malignant cells on the surface of such lesions. In the advanced tumor with ulceration and necrosis, only occasional recognizable cells may be desquamated. Since our primary endeavour is to seek out the earlier cases, these facts emphasize the value of the cytologic method.

SUMMARY

1. The cytologic method of diagnosis has been applied to gastric aspiration in 50 patients with gastric symptoms.

2. A description is presented of the normal and malignant cells which are noted in gastric fluid.

3. Of 24 patients proved to have carcinoma of the stomach, smears were positive in 15 instances.

4. Of 7 patients with resectable lesions of the stomach, smears proved to be positive in 5 cases.

5. Of 26 patients without cancer, the smear was reported positive in 1, a man with a benign gastric ulcer.

6. Two patients had extremely early malignant lesions. In both the lesions were detected by the cytologic technique.

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THE SYNDROME OF OVARIAN PAIN AND INSUFFICIENCY

The Importance of Conserving Ovarian Tissue

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UNLESS it occurs regularly at the time of ovulation, ovarian pain is likely to be overlooked or misdiagnosed. Thus cyclic ovarian pain, or *Mittelschmerz*, described long ago by German gynecologists and more recently believed to be associated with ovulation, has been generally recognized, but the irregular pain of ovarian origin in the absence of demonstrable pelvic disease has not been considered. It is the purpose of this paper to show by the review of carefully observed cases an association of ovarian pain with ovarian dysfunction and to indicate, partly by analogy with known reactions of the ovary in animals, the possible mechanism of the ovarian failure.

Obviously if there is any possibility of an association of ovarian pain and ovarian insufficiency, ovarian tissue should be conserved. It would seem redundant to say that ovarian tissue should be saved, for no one would hold that any tissue should be removed unless it is abnormal, or useless and potentially abnormal. But the protean nature of the ovary makes it subject to mutilation and removal by those unfamiliar with ovarian physiology and pathology. Graafian follicles and corpora lutea, varying greatly in size, are all too frequently mistaken for cysts, and innocuous cysts of the follicle or corpus luteum, resulting perhaps from a temporary upset in the endocrine mechanism, lead to the removal of the entire ovary. Many women suffer no ill effects from unilateral castration, but there are others in whom there appear signs of ovarian failure. If pain in the ovary, because of which perhaps the ovary was removed, was associated with ovarian insufficiency in the intact woman, loss of half of her already inadequate ovarian tissue will make matters worse; pain may develop in the remaining ovary and such symptoms of ovarian insufficiency as she may have had are sure to be aggravated. The inadvisability, because it is unnecessary, of removing small ovarian cysts has been pointed out (13), and the dangers of this procedure have been noted (9). The possible implications of the removal of ovarian tissue can be realized only when one considers the known reactions of the ovary in animals to experimentally induced ovarian insufficiency.

It is known that in animals which have had one ovary removed the remaining ovary increases in size and sheds a greater number of ova. Beyond a certain point, however, removal of ovarian tissue results in disturbed ovarian function. If much more than half of the ovarian tissue is removed, that is, one ovary and part of the second, failure of ovulation and cystic changes result (10,11). A certain mass of ovarian tissue, probably varying in different individuals, must be present in order for it to hypertrophy adequately and restore the disturbed endocrine balance.

It is apparent that in the woman removal of one ovary results in the increased activity of the remaining one, for the menstrual cycle is not usually altered by the operation. The remaining ovary almost immediately does the work formerly accomplished by two. It is not so apparent, however, and not generally recognized by clinicians, that the remaining ovary increases in size while performing the added function. It is also not realized by many who remove ovarian tissue that there is a limit to the amount that can be removed beyond which seriously disturbed function associated with cystic changes occurs. The following case is illustrative:

H. C. When this 25 year old woman was first seen, she complained chiefly of persistent vaginal spotting for the past 20 days. Menstruation, regular until the present episode, had begun at the age of 11.

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She had been married 3 years, there were no pregnancies.

Two years previously she had a right salpingo-oophorectomy because of pain in the right lower quadrant of the abdomen. Two years before that, she had had an appendectomy because of similar pain. Four months before she was first seen, her left ovary had been resected.

Physical findings were negative. During the next 2 weeks, the patient began to experience hot flashes. The spotting, which increased gradually in amount, stopped after a total duration of 38 days. Spotting recurred 10 days later, and it was followed in 2 weeks by a profuse menstruation.

The diagnosis and findings at the first operation when the right ovary was removed could not be learned, but examination of the hospital record covering the second operation, 4 months previously when part of the remaining ovary was removed, revealed that the operation was done because of a supposed mass on the right side which proved to be caused by postoperative adhesions. The left ovary was described as 3 to 4 times the normal size. Apparently because of this enlargement, two-thirds of it were resected. Examination of the slides prepared from the tissue removed revealed entirely normal ovarian tissue, including many graafian follicles and a fresh corpus luteum. The loss of ovarian tissue was progressive. With one ovary, apparently normal function continued, and the ovary increased in size. Unmistakable signs of failure followed further reduction of the ovarian tissue.

This case illustrates for the woman the condition which has been called *extreme partial castration*. In the woman, as in animals, ovarian fragments may not be able to assume the function of the original ovarian mass.

The importance of growing follicles for normal ovarian function has been demonstrated in the rabbit. Westman (24) and Westman and Jacobson (25, 26, 27) have shown that an adequate amount of estrogen produced by the growing follicles is necessary for the occurrence of ovulation and formation of the corpus luteum, that the life of the corpus luteum is dependent upon estrogen, and that these effects are independent of the hypophysis, indicating a direct effect on the ovary. In Westman's experiments, when all but one of the graafian follicles were destroyed, ovulation did not occur in that one even in the presence of a sufficient quantity of gonadotrophic hormone. But when estrogen was added ovulation occurred and a corpus luteum was formed. In view of this action of estrogen in experimentally induced ovarian insufficiency in the rabbit, it would seem reasonable to treat with estrogen ovarian insufficiency in young women with the purpose of improving the function of the ovaries in spite of the widespread opinion that this hormone, produced by the ovary itself, has no direct effect on it. The ovary is peculiar in that it represents two endocrine glands having their maximum activity at different times. The graafian follicles which produce one hormone, estrogen, are followed in the cycle by the corpus luteum which makes another, progesterone.

Westman's experiments indicate that the corpus luteum is dependent on the production of estrogen by the follicles throughout the cycle. The amount of estrogen given and the timing of the administration would be important in therapy aimed at improvement of ovarian function in the woman for it is known that the hormone given in sufficient amount early enough in the cycle will inhibit ovulation, presumably by suppressing the gonadotrophic activity of the hypophysis (21).

The cases to be presented below are divided into 3 groups for analysis. In the first group ovarian tissue had been previously removed, in most instances because of pain in the lower abdomen. Pain recurred following operation and when the patients came under observation of the author its source could be identified as the ovary. In the second group the patients were observed before any surgery was performed. In all of them careful observation revealed the ovary to be the source of the pain and in none was it of sufficient cyclic regularity to be classed as *Mittelschmerz*. Cases of cyclic intermenstrual pain or *Mittelschmerz* comprise the third group.

The frequency with which signs of ovarian insufficiency were associated with ovarian pain suggested that the latter is part of a syndrome of ovarian insufficiency. When looked for, pain and excessive tenderness of the ovary were found frequently enough to be considered criteria of this condition. The beneficial effect of estrogen in the treatment of many of these cases strengthened this impression, and the relief of *Mittelschmerz* without suppressing ovulation, illustrated by the cases in group 3,

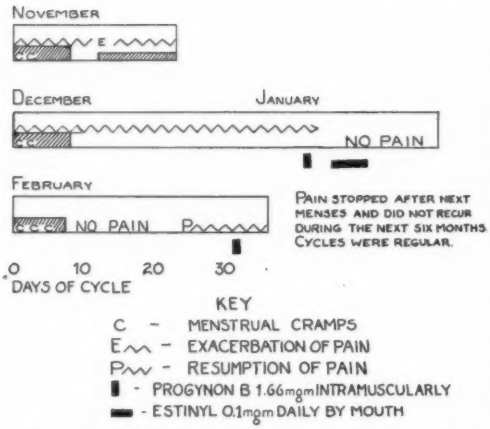

Chart 1. K.M. aged 30. Large rectangles indicate menstrual cycle; small shaded rectangles indicate menstrual flow.

supports the theory that the human ovary, like that of the rabbit, requires the estrogen produced by the growing follicles for completion of the cycle of follicular growth, ovulation and corpus luteum formation and survival, and the quantity of estrogen, and hence the amount or mass of ovarian tissue is of the greatest importance.

Group 1. Ovarian insufficiency and pain following loss of ovarian tissue. There are 15 patients in this group, none of whom was permanently benefited by the removal of ovarian tissue. Pain recurred in all, and 13 of them experienced other symptoms of ovarian failure after operation. Pain was relieved by estrogen in most of the cases in which it was tried, 10 out of 11. One case considered the most typical is described in detail.

K. M. This 30 year old woman began to have recurrent pain in the right lower quadrant of the abdomen at the age of 12, about a year after the menarche. It was frequently associated with nausea and vomiting, and 3 years later an appendectomy was done because of it. Attacks of pain continued. She was first seen in the Out Patient Department at the age of 15, about 8 months after the operation. Menses lasting 4 days were at 28 day intervals. Findings were normal except for abdominal tenderness in the right lower quadrant. The introitus was normal and the hymen was intact. At this time the pain was irregular, described as sharp and shooting, occurring as often as several times a week and lasting as long as a day. During the next 8 years intermittent pain continued but was less troublesome. She married and at the age of 22 had a normal pregnancy with a normal living child. Seen again about a year after her delivery, she again complained of pain in the right lower quadrant, now beginning 2 days after the cessation of the menses. Menses were at 24 to 26 day intervals, lasting 4 to 5 days without dysmenorrhea. Examination revealed ovaries of normal size, the right unusually tender. Three months later the left ovary was more tender, and 3 months after that the right ovary was again described as the more sensitive. At no time was there any evidence of infection. She was not seen again in this clinic until 5 years later. She now complained of pain on the left side, and she reported that 3 years before, 2 years after her last visit, her right ovary had been removed at another hospital because of the pain previously complained of. After the operation she began to have biweekly bleeding and she experienced hot flashes. She also began to have menstrual cramps for the first time. About 6 months after the ovariectomy the pain in the other ovary began. Inquiry revealed that exacerbations of the pain in the left lower quadrant occurred in about mid-cycle along with bleeding. The pain was present most of the time, however, and in the acute phase it radiated down the left thigh, across the pelvis, into the upper abdomen and to the lumbosacral region on the left. Examination was negative except for the extreme tenderness of the left ovary estimated to be 5 centimeters in diameter. The anamnesis during 4 months in this case is shown graphically in Chart 1.

Examination of the slide made from the right ovary, removed 3 years before, revealed normal ovarian tissue.

Reactions like those illustrated in this group of cases have been observed by Karnaky. He mentions 89 cases in which irregular menstruation, flooding, and pain in the left ovary followed removal of the right ovary at the time of appendectomy.

Group 2. Irregular ovarian pain. The 75 patients in this group all experienced pain in one or both lower quadrants of the abdomen for periods ranging from 2 weeks to 10 years. Increased tenderness of the ovary, or in the region of the ovary, on the affected side was demonstrated in all. In none was there any evidence of abnormal ovarian enlargement or adnexal disease. Both ovaries were palpable in 36 cases. In 19 only one could be felt and in 20 neither one could be outlined. In 9 cases it was possible to check the findings at laparotomy.

The onset of pain occurred as early as the ninth and as late as the thirty-eighth year. The largest number of patients, 35, first ex-

perienced pain in the third decade. Twenty-six first noticed pain between the ages of 10 and 20. Onset occurred in the fourth decade in 13 cases. One woman of 21 began having recurrent pain before puberty at the age of 9 years. In 9 cases the pain was cyclic at first and later became irregular. One of these, operated upon in an early attack of pain in the right lower quadrant, was found to have intraperitoneal hemorrhage from a ruptured graafian follicle. This was the only patient of those subjected to laparotomy in whom this condition was found. Suture was not necessary, and the ovary was left alone. Irregular pain began during the following year.

Signs or symptoms of ovarian insufficiency were present in 59 cases. Hot flashes occurred in 27 cases, intercyclic bleeding in 19, abnormally irregular cycles (2 weeks to 2 or 3 months) in 16, menorrhagia in 12, hypomenorrhea in 9, and amenorrhea in 3. Thirty-six patients had one of these symptoms, 19 had 2, and 4 had 3. Sixteen patients had none. The pain was classed as slight in 7 cases and as moderate to severe in 68. In 9 of the latter group, with severe pain, laparotomy was done. There were other signs of insufficiency in all of these; 6 had 1, 2 had 2, and 1 had 3. Three of the 7 patients with slight pain had amenorrhea; 1 had irregular cycles.

Pain occurred most frequently on the right side. In 46 of these 75 cases it was exclusively on the right. In 7 it was experienced only on the left. Either side (one side for a time and then the other) or both sides were involved in 22 cases. Of these the right was the more troublesome in 19, the left in 3.

Fifty-eight patients had menstrual cramps of varying severity. In 21 cases the ovarian pain was aggravated at the time of the menses. In 50 cases it was not, and in these the pain was likely to be less troublesome during menstruation.

Thirty-six patients experienced radiation of the pain into the thigh on the affected side. More may have had this symptom, for the information was not always volunteered when the pain was not severe, and in the early cases patients were not questioned concerning it. The pain was not well localized. Except in severe cases where it radiated to the foot, it usually did not extend beyond the knee. It is of interest that radiation into the thigh of pain of ovarian origin was noted 70 years ago (6). In 10 patients pain seemed to radiate to the back in the sacroiliac region of the affected side.

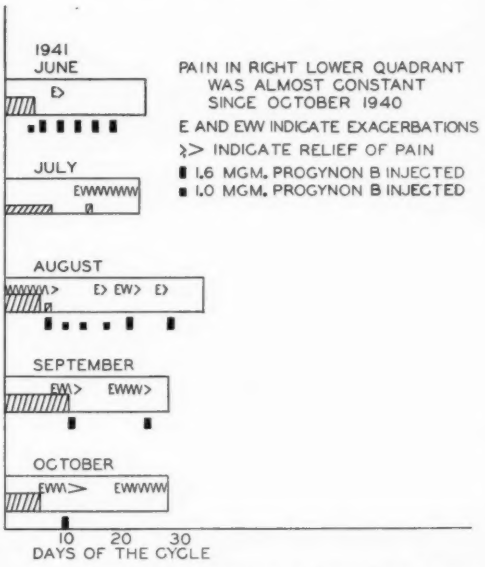

Chart 2. M.M. Large rectangles indicate the menstrual cycle; small shaded rectangles, the menstrual flow.

Two cases of irregular pain are reviewed in detail. The first is one of acute onset of pain in a young woman. The pelvic organs were examined at laparotomy, and a biopsy of the painful ovary was obtained, but long-term follow-up was not possible.

D. S. This 20 year old woman complained of intermittent, and at times incapacitating pain in the right lower quadrant of the abdomen for the past 10 days. Her last menstrual period occurred 2 days after the pain began and lasted one day. The pain became worse after the one day flow, and at the time she was first seen it was almost constant. Her appendix had been removed.

Menarche at 12, her periods had been of 3 days duration at 28 day intervals until 3 months before, when they became shorter, only 1 day, and were accompanied by more pain, consisting of lower abdominal cramps. General examination was negative except for tenderness in the right lower quadrant. Pelvic examination revealed a very tender mass the size of a normal ovary on the right side. Rabbit ovulation test for pregnancy was negative.

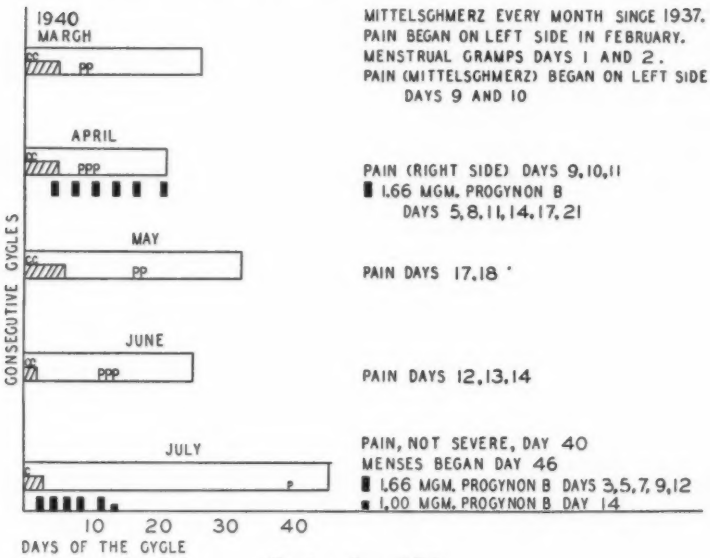

Chart 3. Case of F.S.

Because of the negative findings, the patient was observed. The pain, however, became more severe, and on examination 2 days later, the mass on the right, thought to be ovary, was more tender, so much so that operation was decided upon.

At operation, the pelvic organs were found to be normal in appearance. The right ovary, larger than the left, and apparently the mass which had been felt on examination, was not over 5 centimeters in its greatest diameter. It appeared tense, however, and on incision, several follicles were found in the central portion. The largest of these were carefully resected, and the incision was closed with fine catgut. No corpora lutea were identified in either ovary.

Histological examination of the tissue removed showed normal ovarian tissue including cellular stroma, the walls of several graafian follicles, and part of a corpus albicans.

There was no recurrence of pain during the 2 weeks following operation.

This case is the type in which one ovary, the apparent source of incapacitating pain, is likely to be removed.

In the following case operation was avoided in an early acute attack of pain. The subsequent course over a period of 2½ years is summarized.

M. M. This unmarried woman was first seen in 1941 at the age of 22. She had experienced recurrent attacks of pain in the right lower quadrant of the abdomen for 5 months. The first attack occurred midway between two menstrual periods and was accompanied by scant bleeding of 3 days' duration. The next attack, a month later, was unaccompanied by bleeding. It was of such severity, associated with nausea, that appendicitis was suspected. Vital signs were normal, however, and the classical signs of appendicitis were lacking. Since then, attacks had become more frequent, and she had almost constant soreness in the right lower quadrant, aggravated by walking. For the past 5 days, there had been scant vaginal bleeding which had begun 2 to 3 weeks after the last menstrual period. She complained also of some pain in the right sacroiliac region.

The menarche had occurred at the age of 14, and periods had been irregular, 14 to 35 days, lasting 8 to 10 days. She always experienced crampy pelvic pain during the flow, preceded for a few days by aching in the right lower quadrant like the pain of which she complained. The flow was often excessive, and she frequently remained in bed during the first day. General physical examination was negative. On pelvic examination, the right ovary was found to be markedly tender although within normal limits of size. Basal metabolic rate was −13 per cent. The patient was observed during the next 2 years, during which pain was intermittent and menstrual irregularity persisted. Treatment consisted principally of small doses of thyroid over long periods and injection of estrogen, 1 or 1.6 milligrams of progynon B at various times during the cycle. Injections were almost always followed by relief of the pain, at times for as long as a week, but usually for a day or two. On more than one occasion, when the estrogen was given frequently in the early part of the cycle, men-

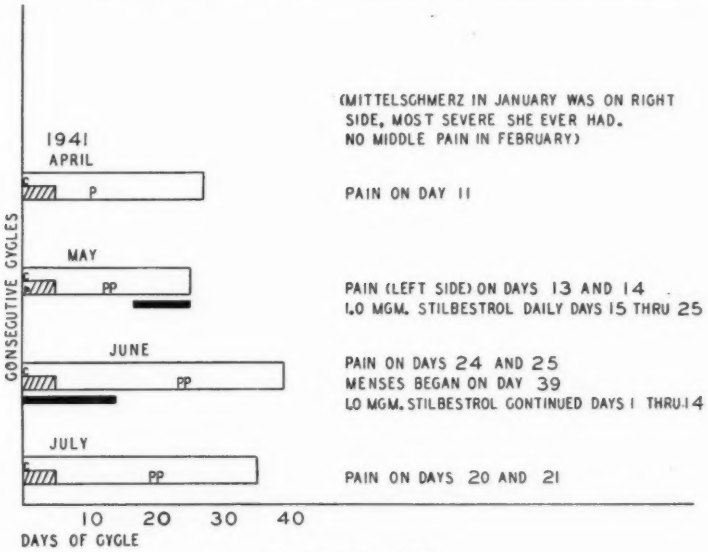
(MITTELSCHMERZ IN JANUARY WAS ON RIGHT SIDE, MOST SEVERE SHE EVER HAD. NO MIDDLE PAIN IN FEBRUARY)
1941
APRIL
P
PAIN ON DAY 11
MAY
PP
PAIN (LEFT SIDE) ON DAYS 13 AND 14
1.0 MGM. STILBESTROL DAILY DAYS 15 THRU 25
JUNE
PP
PAIN ON DAYS 24 AND 25
MENSES BEGAN ON DAY 39
1.0 MGM. STILBESTROL CONTINUED DAYS 1 THRU 14
JULY
PP
PAIN ON DAYS 20 AND 21
CONSECUTIVE CYCLES
10 20 30 40
DAYS OF CYCLE

Chart 4. Case of F.S.

strual cramps were abolished, indication that ovulation had been suppressed.

Typical responses of the ovarian pain to estrogen are shown in the diagram of 5 consecutive cycles in Chart 2. The pain began as rather typical *Mittelschmerz*, but after 2 months it became practically constant. Exacerbations frequently occurred in midcycle, however, when ovarian activity would be expected to be at a peak. This patient married in 1946. A year later she had a normal pregnancy resulting in a full term child. Pain continued irregularly through the early months of pregnancy, but ceased after about the fifth month.

Administration of estrogen was followed by relief of pain in 3 out of every 4 cases in this group. It was tried in 53. No effect was observed in 14. In 39 there was relief, and 23 of these were classed as remissions since symptoms were definitely improved for more than a week. The reaction to estrogen could usually be determined by injection of 1.0 to 1.6 milligrams of estradiol benzoate (see Chart 2). In 2 cases pain became cyclic following treatment with estrogen.

Anyone who has tried to evaluate the effect of a therapeutic agent administered for the relief of subjective symptoms realizes the difficulty of convincing himself that any improvement is not the result of suggestion. The menstrual aberrations, however, improved along with the pain, and injection of other substances was without similar effect. The degree of relief appeared to vary with the dosage. The benefit from 1.6 milligrams of progynon B was often obviously greater than from .33 milligram. Pain was increased by chorionic gonadotropin and that of pregnant mare's serum.

In the most severe cases where the pain was constant and incapacitating, just as in an attack of *Mittelschmerz*, estrogen was ineffective. Indeed, when most needed it did not help. These cases present a very difficult problem. Ovarian specimens were taken for biopsy and the albuginea was cut in 2 cases with only temporary relief. Four cases in group 2 were treated with bilateral section of the ovarian plexus and vessels as described by Bigelow. There was temporary relief in 3, but the longest remission was only a month. In one case the pain became cyclic and it has remained so for more than a year. Two of the patients who experienced temporary relief from section of the ovarian plexus were further treated with presacral and bilateral lumbar sympathectomy (removal of the first to the fourth sympathetic ganglia on both sides). Both patients developed pain again after several

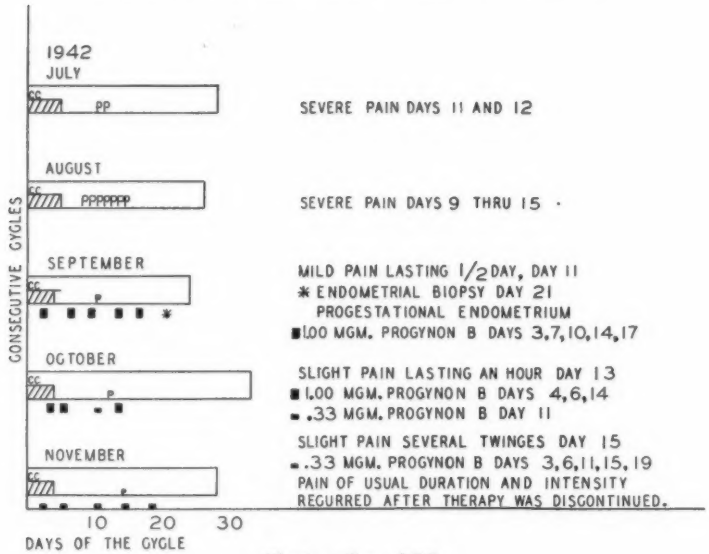

Chart 5. Case of F.S.

months of relief. In one it was on the opposite side. The pain has been less severe in both patients, however, and one has become pregnant.

The similarity of the symptoms and signs of this condition to those of chronic inflammatory disease is great. In some patients with long hospital records the diagnosis of salpingitis had been made, but it was found to be unproved at the time and subsequent findings made it untenable. In most of the patients with repeated hospital admissions diagnosis of abdominal pain, cause undetermined, had been made. Endometriosis also has features in common with this condition, and it was considered particularly in those patients in whom the pain was aggravated by the menses. Unlike endometriosis, pelvic findings are normal in these cases even after many years of symptoms. There does not appear to be any unusual infertility.

It will be noted that pain in the right ovary is much more frequent than in the left. This suggests that the right ovary is the more active. This may be true. That the two ovaries are not equally functional has been noted (2). In 64 cases of cesarean section in which he could find it, Williams noted the corpus luteum in the right ovary 36 times and in the left 28 (29). Presumptive evidence of the side on which ovulation occurred may be gained from the location of tubal and ovarian pregnancy. Ward Ekas found in a review of the cases of ectopic pregnancy at the Strong Memorial Hospital that in 180 cases it occurred 104 times on the right side and 76 on the left. According to Hartman ovulation occurs more frequently on the right side in the monkey.

Group 3. Cyclic intermenstrual pain or Mittelschmerz. The similarity of the pain so far described with *Mittelschmerz* is apparent. In 5 of the 15 cases in group 1 the pain which followed removal of one ovary was cyclic, and it is of interest that in the first case described by Wharton and Henriksen in their paper on periodic intermenstrual pain, typical *Mittelschmerz* made its appearance after the removal of one ovary.

Eleven of 25 unselected cases of *Mittelschmerz* had signs of ovarian dysfunction. There was intercyclic bleeding in 8, menorrhagia in 2, and hot flashes in 2. The occurrence of intercyclic bleeding with *Mittelschmerz* has been noted (22). In 8 cases treatment with estrogen was followed by relief of pain. Ovulation at times was prevented by large doses. In fact the original intention was

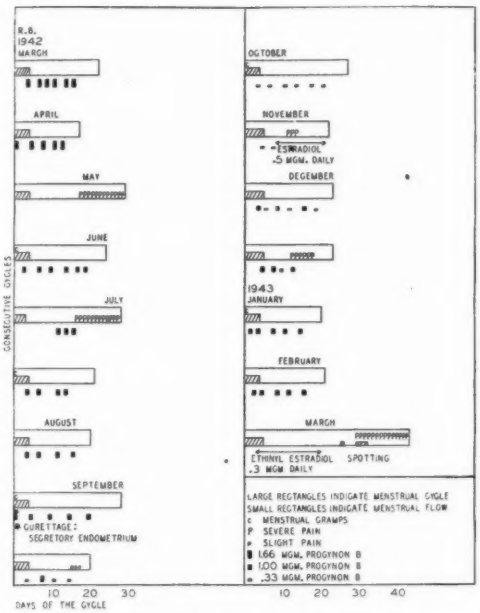

Chart 6. Case of R.B.

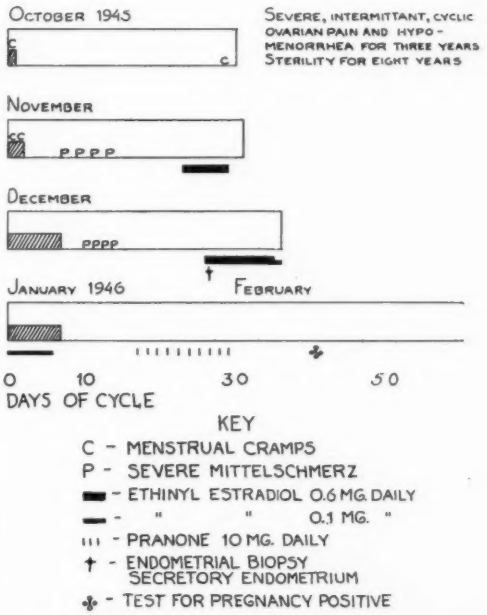

Chart 7. Case of H.R., aged 29. Spontaneous abortion occurred on June 24.

to give the patient relief from severe and prolonged pain by prevention of ovulation. But with smaller amounts, pain in some cycles was reduced to insignificance, suggesting that ovulation was not prevented, and in other cycles where there was no pain at all endometrial biopsy indicated that ovulation had occurred. Two cases treated with estrogen are described.

F.S. This woman, tripara, began to have *Mittelschmerz* in 1937, when she was 32 years old. The pain occurred on either side 9 to 17 days after the onset of the menstrual period and usually lasted 2 or 3 days. *Mittelschmerz* began 3 years after the birth of her last child. Pelvic findings were normal.

Periods of observation and treatment in 1940, 1941, and 1942 are illustrated in Charts 3 to 5. The importance of the amount of hormone given and the timing of the administration is shown. In April 1940, doses of estrogen, progynon B, sufficient to suppress or postpone ovulation were begun too late in the cycle to have any effect. A slightly smaller amount of the same hormone, begun earlier and given more frequently the following July, resulted in lengthening the menstrual interval to 45 days, indicating suppression or postponement of ovulation.

In January, 1941, she was confined to bed with the most severe pain of her experience. The next month there was no pain, probably indicating an anovulatory cycle, rare for this individual. Pain recurred the next month. In May, stilbesterol by mouth, 1 milligram daily, was begun after the *Mittelschmerz* and continued through the 16th day of the next cycle. Typical pain occurred 10 days later, on the 24th and 25th, 16 days before the onset of the following menses. The following month pain occurred on the 19th and 20th days, again 16 days before the onset of the next menses. Previously recorded *Mittelschmerz* had not been later than the 17th day. Ovulation seemed to have been postponed in June by the administration of estrogen.

In August, 1942, the patient again sought relief of her *Mittelschmerz*, attempts at which had been futile until now, because of the unusual persistence that month of the pain which lasted an entire week. Progynon B was again tried, in a slightly smaller amount than previously, injections of 1.0 milligram rather than 1.66 milligrams, begun on the third day of the cycle in September and repeated on the 7th and 10th days. Only slight pain, lasting about an hour occurred on the 11th day. Since it was not certain that the pain represented *Mittelschmerz*, estrogen was given again on the 14th and 17th days. That the pain was *Mittelschmerz*, modified by the therapy, was indicated by the occurrence of menstruation 14 days later, and, more important by the presence of a normal progestational endometrium revealed by endo-

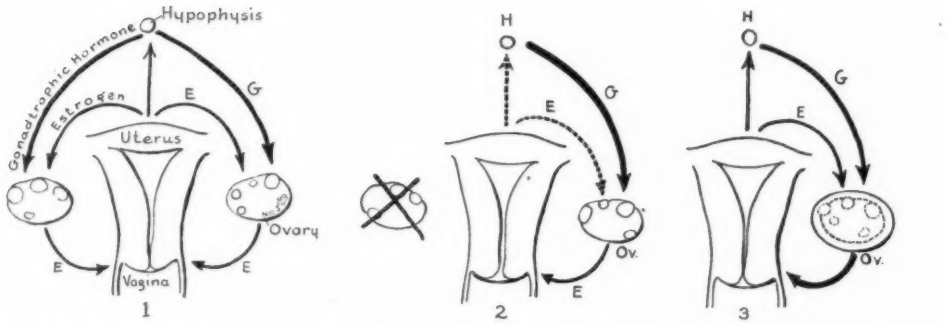

Fig. 1.[1] Normal balance. The proper proportion of estrogen and gonadotrophic hormone is necessary for ovulation. By its effect on the hypophysis estrogen is keeping the production of gonadotrophic hormone in check. The uterus removes from the circulation an amount of estrogen determined by its size.

Fig. 2. Loss of one ovary. Because of the decrease of estrogen, there is increased production of gonadotrophic hormone.

Fig. 3. Remaining ovary enlarges, restoring the balance. In response to the increased gonadotrophic stimulus, more follicles become active. If there is enough ovarian tissue remaining, the estrogen output increases sufficiently to restore the balance and normal function ensues.

metrial biopsy on the 21st day. Similar results were obtained during the next 2 months by the administration of relatively small doses of estrogen. In December, 1942, when no therapy was given, pain of the usual intensity promptly recurred, and it continued regularly at least until 1945. There were, however, no attacks as prolonged as that in 1942.

R.B. In January 1941, at the age of 26, this nulliparous, married woman began to have crampy, midpelvic pain tending to the right side, occurring in the middle of the interval and usually lasting until the menstrual flow began. Menses had been fairly regular around 4 weeks since the onset at the age of 11, and lasted 5 days. She often had menstrual cramps the first day of the flow.

Pelvic examination revealed two small fibroids, estimated at 2 centimeters in diameter. Otherwise examination was negative.

In March, 1942, estrogen therapy was begun as indicated in Chart 6. The original intention was to prevent ovulation, and this seems to have been accomplished at first, March-April, 1942, when 1.66 milligram doses of progynon B were given. Later, smaller doses were given with equally good results, and it became apparent that the beneficial effect was not dependent on the suppression of ovulation when endometrial biopsy on the first day of the flow following a painless interval, August, revealed secretory endometrium. The occurrence of menstrual cramps after the relief of the *Mittelschmerz* is also significant, for although cramps on the first day of the flow are not a constant occurrence, they would not be expected to occur in the absence of ovulation (21).

It will be noted that where injections were begun before the 5th day, pain was obliterated or relieved, and this was accomplished with as little as .33 milligram of progynon B twice weekly (October). The postponement of ovulation by too large a dose of estrogen is illustrated by the last cycle on the chart, February-March, 1943. Ethinyl estradiol (Estinyl) .3 milligram daily from the 4th through the 20th was followed 9 days later by the pain accompanied by estrogen withdrawal bleeding, and the cycle lasted 43 days.

A third case H.R. is illustrated in Chart 7. Here there was no *Mittelschmerz* following treatment with estrogen, and ovulation was proved by the occurrence of pregnancy. The relief of dysmenorrhea and the sudden change in the fertility of this patient also indicate improved ovarian function.

ETIOLOGY OF OVARIAN PAIN

It would be specious to represent the two types of pain, cyclic and irregular, as essentially different. They are probably different manifestations of the same process. That other signs of ovarian dysfunction are seen more frequently with irregular pain than with *Mittelschmerz* suggests that the former is a manifestation of a more serious dyscrasia. The occurrence of *Mittelschmerz* early in the history of some of the cases of irregular pain and its appearance after therapy in others, as well as the exacerbations of pain in midcycle, indicate a close relationship between the two types.

The nature of the underlying disorder is obscure. Ovarian tissue removed from the 2

[1]All of the diagrams represent the same phase of the cycle, that of follicular growth preceding ovulation. Only one gonadotrophic factor, the follicle stimulating, is considered.

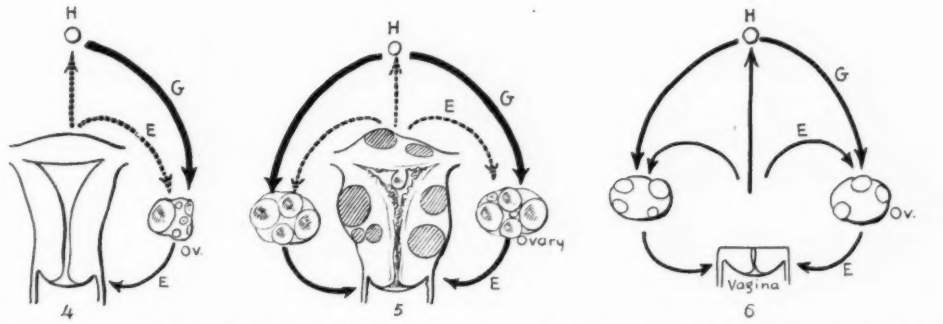

Fig. 4. Extreme partial castration. With the loss of much more than half of the original ovarian tissue, that remaining is inadequate and cannot produce the needed estrogen. The imbalance persists, and because of insufficient estrogen there is failure of ovulation. Persistent follicles and cystic changes result.

Fig. 5. With tumors of the uterus, the use of estrogen may increase to the point where an effect similar to that resulting from loss of too much ovarian tissue is produced. The ovaries enlarge to capacity and then fail because of insufficient estrogen.

Fig. 6. Hysterectomy spares estrogen. It may relieve the condition which is illustrated in Figure 5 for a temporary period of time, but function ceases after a while because the uterus keeps the cycle going by its periodic use of estrogen.

cases in group 1, and the biopsies from 3 cases in group 2, revealed little which at present can elucidate the problem. In 2 of the biopsies a superficial overgrowth of fibrous tissue was noted, possibly supporting the idea, readily arrived at intuitively, that pain is caused by too resistant ovarian fibrous tissue (tunica albuginea). If the albuginea were too dense there would be abnormal pressure as follicles increased in size, and if the follicular growth were thus impeded, production of ovarian hormones would be reduced. Both the pain and the dysfunction might be explained in this way. The condition described by Goodall as chronic cystic ovarian sclerosis may, in varying degrees, account for this syndrome. Estrogen may produce its beneficial effect by improving the blood supply of the ovary.

THEORETICAL CONSIDERATIONS

The occurrence of pain in the remaining ovary after the removal of one ovary along with the appearance or aggravation of other signs of ovarian insufficiency, the beneficial effect of estrogen, and the ovarian failure resulting from extreme partial castration exemplified by case H.C. have inspired the hypotheses illustrated in Figures 1 through 7.

The uterus should be considered in any theory of ovarian function, for its removal is followed first by an apparent increase, and later by an early decline of ovarian activity. The increase is indicated by the prolongation of the life of the corpus luteum by hysterectomy (12). This is explained by the estrogen sparing effect of that operation. The supply of estrogen is greater following excision of the uterus, which when present removes estrogen from the circulation (8). Hysterectomy not only spares estrogen, however, but it results in the early cessation of the ovarian cycle (16, 17, 18, 4). It seems that in order to function the ovary must be stimulated intermittently. Decline of ovarian activity earlier than normal after hysterectomy may be explained if one assumes that the use of estrogen by the uterus is cyclic, and that wide fluctuations of estrogen and gonadotrophic hormones, observed in normal women (23), are necessary for normal ovarian function. Removal of the uterus results in decreased fluctuations in the level of estrogen and is therefore followed by earlier ovarian failure. By the periodic growth of the endometrium, the level of circulating estrogen is made to fluctuate. The periodic changes in estrogen concentration cause fluctuations in the hypophyseal gonadotrophic hormone which in turn stimulates the ovary intermittently. Thus the uterus takes an active part in the functional balance of ovary and pituitary. One may think of the uterus as the balancer on a seesaw having the

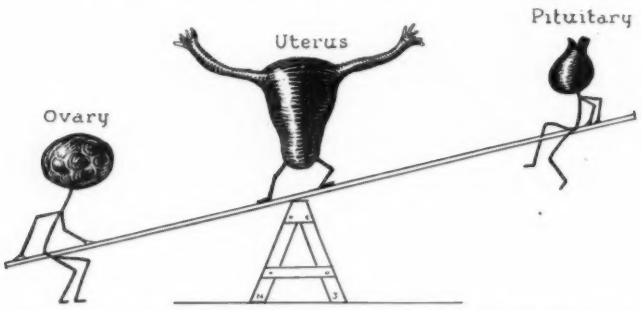

Fig. 7. Normal function may be thought of as maximum activity of a seesaw. If any of the members gets out of balance inadequate activity results and normal function ceases. Large periodic fluctuations in the amounts of estrogen and gonadotrophic hormone are necessary for normal function, and the uterus enhances the fluctuations by its periodic use of estrogen.

ovary on one end and the pituitary on the other. When the uterus is absent, motion of the seesaw, representing function, becomes feeble and then stops, just as it does if either of the riders on the seesaw stops working (Fig. 7).

Normal function may be thought of as violent or maximum action of the seesaw, various degrees of abnormal function as grades of inadequate activity. Observed relief of functional gynecological disorders with practically any procedure and therapeutic agent can be rationalized if one thinks of them as improving the action of the seesaw. Measures which have been reported to be beneficial include curettage, x-ray to ovaries and hypophysis, injections of gonadotrophics and male as well as female hormones. Anything which sufficiently stimulates or suppresses the hypophysis or the ovary, directly or through the nervous system, or has an effect on the estrogen utilizing capacity of the uterus may improve the action of the seesaw. Large amounts of estrogen may stop feeble activity altogether by suppression of the hypophysis and make possible a rebound of maximum activity after release of the inhibition. The beneficial effect of 5 milligrams of stilbesterol daily for 20 days in ovarian dysfunction observed by Karnaky and Patton may be explained in this way. The relief of the sterility as well as the *Mittelschmerz* and dysmenorrhea of H.R. in group 3 may thus have resulted from the improved ovarian function produced by a large amount of estrogen.

According to this theory an amount of estrogen sufficient to affect the hypophysis but not enough to suppress it altogether might be expected to dampen the ovarian cycle and result in abnormality. It would neither stop the pituitary-ovarian seesaw, allowing for a later rebound, nor would it boost its activity. Ovarian dysfunction would result. This is illustrated by a case described by D'Amour and Woods in which dysfunctional bleeding occurred in a normal woman following daily administration for 2 months of .04 milligram of estradiol by inunction.

The experiments of Westman, mentioned earlier, indicate that estrogen is necessary, apart from any effect on the pituitary, for normal ovarian function. It is perhaps pertinent that synergism of estrogen with gonadotropins in effects of the latter on the ovaries of hypophysectomized rats has been observed (30, 15, 19). Both gonadotropin and estrogen are needed for ovulation and the formation and survival of the corpus luteum. Figures 1 through 4 illustrate a theoretical synthesis of this with the work of Lipschutz, showing that on the removal of ovarian tissue relatively more follicles in the remaining tissue are stimulated to activity, and function remains normal up to a certain point, but after too much has been removed function ceases and the ovarian remnant becomes cystic. The mechanism of the ovarian failure of extreme partial castration, illustrated in Figure 4 may be the same as that associated with lesions of

the uterus which result in increased removal of estrogen from the circulation (Fig. 5 through 7). The association of menstrual irregularities and cystic ovarian changes with uterine fibroids has long been recognized. It has been suggested that the cysts may be the cause of the tumors by the production of excess estrogen (31,32), but it is possible that the uterine tumors disturb the ovarian function by lowering the estrogen to a point where an effect is produced comparable to that caused by the loss of too much ovarian tissue (see Figs. 4 and 5). In the case of growing tumors of the uterus, one would expect a gradual increase in the activity of the ovaries until the limit of their ability to produce more estrogen is reached, following which the signs of failure would begin. The nature of the tumors, some containing more muscle tissue than others, and their location, some encroaching on and causing an increase in the amount of endometrium, would determine their thirst for estrogen and explain the variation in the effects of these tumors in different individuals.

A case which is described by Wharton and Henriksen in their paper discussing periodic intermenstrual pain supports this hypothesis. Intermenstrual pain without ovulation, a sign of ovarian failure, ceased after removal of a myomatous uterus. Description of the case is quoted.

"A Jewess, aged 30, began to menstruate at the age of 13; the menses had always been regular, every 28 days, lasting from 6 to 7 days, with profuse flow. She had conceived normally in 1930. Intermenstrual pain accompanied by spotting began in 1933. She was operated on at the Sinai Hospital in July, 1935, because of uterine myomas with profuse menstrual hemorrhage. We performed the hysterectomy deliberately on the second day of the intermenstrual pain and spotting, 9 days after the close of the last menses, expecting to find signs of ovulation. The ovaries, however, showed no evidence whatever of graafian follicles or corpora lutea; in short, there was no sign of ovulation, although the menstrual cycle had been normal and the patient had the molimina that accompany ovulation. Since July, 1935, she has been completely relieved of the intermenstrual pain and spotting. The pathologic diagnosis in this case was uterine myomas, endometrial hyperplasia with polyp, and endometrial glands invading the uterine wall."

In one case in group 2 the uterus was removed because of prolonged bleeding which did not respond to conservative measures. The pain ceased after hysterectomy although the ovaries remained untouched.

The above considerations have dealt with ovarian insufficiency. Hyperfunction of the ovaries is also possible. The syndrome described by Stein, characterized by hirsutism and amenorrhea, may be caused by hyperfunction of the ovaries for it is relieved by the removal of ovarian tissue. The wedge operation by which it is successfully treated can have little permanent effect beyond the reduction of the ovarian mass.

SUMMARY AND CONCLUSIONS

Ovarian pain can occur in the absence of any demonstrable lesion of the ovary, and it may have no regular relation to the menstrual cycle. Its frequent association with menstrual irregularities indicates that the pain is itself a sign of ovarian dysfunction.

This syndrome of ovarian pain, menstrual aberrations, and other signs of ovarian failure, such as hot flashes, occurs in all ages of reproductive life.

The more frequent occurrence of pain on the right side in these cases in addition to other evidence suggests that the right ovary in women is the more active.

By the presentation of cases in which ovarian tissue has been removed in women and the citing of the known effects of partial castration in animals, the importance of an adequate mass of ovarian tissue for normal function is shown, and the need for conserving ovarian tissue in women is stressed. If one ovary is removed because of this type of pain, signs of ovarian insufficiency and pain in the remaining ovary may be expected.

The beneficial effect of therapy with estrogen including alleviation of cyclic intermenstrual pain without the prevention of ovulation suggests that the importance of the mass of ovarian tissue lies in its production of estrogen.

A theory of ovarian function is presented which includes the rôle of the uterus.

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ENDOMETRIOSIS AS A CAUSE OF INTESTINAL OBSTRUCTION

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ALTHOUGH endometriosis[1] with involvement of the small and large intestine is encountered only occasionally, it occurs with sufficient frequency to justify giving it a position among the important benign lesions of the bowel. It further commands our interest because it represents a benign condition which at times exhibits such infiltrative tendencies as to make its lesions rather easily confused with malignant neoplastic processes. Especially is this true in those occasional circumstances in which extensive invasion of the intestinal wall by the lesions of endometriosis so compresses the lumen of the invaded segment that complete or incomplete intestinal obstruction ensues. The present report deals with a number of such cases seen and studied from the surgical files of the Mayo Clinic. We feel that throughout the literature the importance of this complication has not been sufficiently stressed.

HISTORICAL REVIEW OF CASES

In 1909 Meyer gave a detailed report of a 45 year old woman who required operative intervention for the relief of a lesion which we should now term obstructing endometriosis of the bowel. In 1918 Lockyer referred to this case in his textbook *Fibroids and Allied Tumors*. In 1920 Cullen reported a case of sigmoidal obstruction on the same basis, which has since become more or less classic among writers of modern textbooks of gynecology.

Sampson in 1921, in his definitive paper on endometriosis, described a sigmoidal endometrioma and cleared the field for subsequent recognition of these lesions as local proliferations of ectopic endometrial tissue. In 1923 Judd and Foulds recorded 5 instances of sigmoidal endometrioma, in 3 of which definite degrees of intestinal obstruction were manifest. In 2 of the 3 cases recorded in 1927 by Graves the rectal lumen was compromised. In his third case there was chronic intermittent obstruction of the sigmoid resulting from an infiltrative endometrioma.

A rectal carcinoma was coexistent with a low sigmoidal endometrioma in the case recorded in 1932 by Braine. Endometriosis of the sigmoid portion of the colon produced local obstruction in the case reported in 1935 by Bartlett. In Marmol's case in 1935 a 24 year old woman exhibited signs and symptoms of rectal obstruction resulting from the continual growth of an endometrioma of the rectovaginal septum.

In 1937 Cattell made an important contribution in his report of 17 cases demonstrating involvement of the lower portion of the bowel. Two of 4 patients with sigmoidal endometriosis had almost complete intestinal obstruction. Eight patients exhibited lesions fairly high in the rectum, including its junction with the sigmoid, and all had experienced some degree of "clinical" obstruction. Definite obstruction was manifest in 2 of the remaining 5 instances in which the rectovaginal septum was the seat of involvement.

In 1940 Glenn and Thornton published their observations on 2 patients who had obstructing endometriomas of the ileum. In a review of the literature they were able to find only 4 additional cases in which there was any degree of obstruction on a similar basis.

Two recent cases of intestinal obstruction caused by endometriosis, reported by Thierstein and Allen, along with individual reports of a similar nature by Mouat, Lee, Starr,

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Abridgment of part of a thesis submitted by Dr. McGuff to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

[1]Correct usage dictates that the term "endometriosis" be used to indicate the condition which exists when endometrial tissue is found in any extrauterine location. When the lesions are tumefactive the designation "endometrioma" is often employed.

Schuler, Gale, Goodwin, Behrendt and Neumeyer, Okinczyc, Friedman, Hepburn, Papin, Josefsson, Grigsby, Patton and Patton, Milnor, Blaikley, Morrin, Lukins and Lukins, Ben-Asher, and Wood, Deibert, and Kain comprise the literature on this interesting condition (13, 18, 20, 27, 29), the frequency and the importance of which have not received a merited degree of attention in medical writings of the past 25 years.

MATERIALS AND METHODS

Over the period from 1920 to 1946, inclusive, the surgical files of the Mayo Clinic were found to contain records of 48 cases in which the diagnosis of "endometriosis of the bowel" had been made by a pathologist. In 16 of these 48 cases pathologic material had been removed in an effort to alleviate clinical symptoms and signs of intestinal obstruction caused by cicatrizing endometriosis. The present study concerns these 16 cases.

Material preserved from all of these lesions was secured and studied in gross detail with special reference to such features as the degree of local narrowing of the intestinal lumen, the presence or absence of mucosal ulceration, the degree of spread above and below the point of major impingement as measured by gross induration of tissues, the thickness of the intestinal wall and the amount of reactive fibrosis. In those instances in which wide resection had been performed an estimate was made of the degree and duration of the obstruction by comparing luminal diameters of the bowel above and below the level of the lesion and correlating these with the thickness of the uninvolved proximal and distal segments relative to the muscularis propria. Numerous small representative blocks were cut from different levels and these were placed in bottles containing a fresh 10 per cent neutral solution of commercial formalin. Microscopic sections were then prepared using the paraffin method. Routine hematoxylin and eosin stains were employed in this study but in addition the van Gieson method was used for demonstration of fibrous tissue and a stain using the Prussian blue reaction was utilized in order to bring out the presence of hemosiderin.

CLINICAL ANALYSIS

The average age of the 16 patients who had intestinal obstruction caused by endometriosis was 39.5 years with extremes of 31 and 54 years. Seven patients were in the fourth, 8 in the fifth, and 1 in the sixth decade of life. There were no colored patients in this series of cases.

Ten of the women had been married for periods of from 4 years to 25 years with an average of 11.1 years. Four were single. Two were separated from their husbands.

Symptoms. All of the patients had complained of one or more symptoms for periods ranging from 2 months to 18 years with an average of 6.5 years. As will be shown in subsequent paragraphs many of these symptoms are related to the early stages in the development of the endometriosis. Those relative to the effects of intestinal invasion will be discussed first, as being most pertinent to the problem under investigation.

Four of the patients (all with sigmoidal lesions) were suffering from "complete stoppage" of the bowels at the time of initial examination. In this group the picture was typical of acute obstruction with lower abdominal pain, abdominal distention, and complete obstipation with no passage of feces or flatus. In an additional 6 cases the symptoms pointed to the existence of partial intestinal obstruction of rather severe degree but which allowed the passage of some gas through the point of narrowing. In 3 of these cases the sigmoid portion of the colon, in 2 the rectosigmoidal junction, and in 1 the distal portion of the ileum were respectively the sites of pathologic narrowing by the process. In the remaining 6 cases progressively severe constipation, constipation alternating with diarrhea, abdominal distention, and other symptoms listed subsequently became progressively worse in an intermittent fashion and indicated the progression of gradual narrowing of the bowel. These we classified as cases of chronic obstruction. In 3 of these cases the sigmoid portion of the colon was the seat of the obstruction with the rectosigmoidal segment accounting for another and the distal portion of the ileum as the site of the remaining two lesions.

Considering the group as a whole, moreover, we find additionally that all 16 of the patients complained of cramping abdominal pain. Abdominal distention and severe constipation were prominent in all 10 cases falling into the first two groups listed in the preceding paragraph. Vomiting had occurred as a symptom in 1 of the 3 cases of obstructing endometriosis of the ileum and in 4 of the remainder.

Symptoms which might be attributed in part to the process in its preobstructive stage might be listed as intermittent constipation, noted by 13 patients as being worse at the time of menstruation than at other times. Five of the patients had suffered from intermittent attacks of diarrhea and 4 of these had had alternating periods of constipation and diarrhea. Grossly bloody stools had been noticed by 3 patients. This symptom had been present only with menstruation. Four of the patients had sustained loss of weight, in one case to the extent of 27 pounds (12.2 kg.). It was felt that in these cases abdominal distress resulting from incipient obstruction had led to decreased dietary intake. An earlier group of symptoms are related more to the existence of pelvic endometriosis than to its intestinal complications and are herein mentioned to complete the picture on a chronic basis.

Infertility, relative or absolute, was frequently present and 9 of the patients complained of absolute sterility. The 10 married women in the series had had a total of but 3 pregnancies, only 2 of which terminated with the birth of live children. One of the 4 unmarried patients had had a pregnancy which terminated in (or was terminated by) abortion. Among the 4 women who had been pregnant the average period which had elapsed since the last pregnancy was 14.2 years with extremes of 5 and 23 years. The importance of these findings is further emphasized by the fact that 6 of the 10 married patients mentioned had undergone previous pelvic operations designed in several instances to make pregnancy possible by resecting regions of endometriosis.

Acquired dysmenorrhea was a major symptom in 8 of the 16 cases. In an additional 4 cases the patients did not complain of this symptom. In the remaining 4 cases the records did not supply information on this point. Dyspareunia, surprisingly enough, was not listed as a major symptom by any patient in this group. It was elicited as not being a symptom in 2 cases and in the remainder the records were noninformative. However, 5 of the 13 patients whose lesions were found in the lower segments of the bowel had complained of rectal pain and several others had complained of pain on defecation. Menstrual irregularities, so prominent in cases of pelvic endometriosis, were noted in only 4 of the cases. In 9 the periods were described as being regular, 2 patients had undergone previous hysterectomy and 1 patient had been amenorrheic for 3 years as a consequence of the menopause. Menorrhagia was noted as a symptom 4 times among the group and 2 patients having otherwise normal menses had complained of some intermenstrual spotting.

The aforementioned symptoms, which were relevant to the underlying endometriosis rather than to its obstructive complication, had been present for periods varying from several months to 18 years with an average duration of 6.5 years.

Physical findings in all 16 cases were consistent with the clinical diagnosis of intestinal obstruction. On the basis of an evaluation of symptoms combined with the results of digital rectal and vaginal examination, the correct diagnosis was made preoperatively in 7 of the 16 cases studied.

Sigmoidoscopic examination was performed in 12 cases and in 9 of these positive evidence of luminal narrowing was obtained. In 2 cases, as was proved later, the sigmoidal lesions were beyond the reach of the sigmoidoscope and in the third case in which the findings were negative the lesion was located in the terminal portion of the ileum. In none of the cases was the presence of mucosal ulceration observed. In several cases, however, the sigmoidoscopist remarked on the peculiar puckering of the mucosa over the area of involvement.

In 9 of 11 cases results of roentgenographic study after administration of barium enemas were interpreted as being positive inasmuch as the roentgenograms demonstrated and localized the point of the obstruction. The

two "failures" were in a case in which the lesion was ileal and in another in which the upper portion of the rectum was only mildly obstructed by the endometrioma. By way of offsetting these 2 cases the roentgenologist in 2 of the less "positive" examinations suggested the diagnosis of obstructing endometrioma.

TREATMENT[1]

Fifteen of the 16 lesions were treated surgically by local resection of the bowel and in 1 instance partial excision of the endometrioma was accomplished. The details of the various procedures in the 16 cases follow:

a. When the point of obstruction was in the sigmoid or distal to it. Resection of the bowel was done in 12 of the 13 cases in this group and in 1 the endometrioma was excised. In 5 of the cases complete resection of a segment of the bowel was done and in 1 case the resection of the bowel was partial. In this group of 12 resections of the bowel colostomy was performed 8 times and cecostomy was performed once. In 2 patients in their early thirties in this group myomectomy was performed plus resection of the bowel in a conservative effort to preserve reproductive function. Resection of the lower part of the bowel plus removal of both tubes and ovaries or of the remaining tube and ovary was done in 5 cases. Panhysterectomy plus resection of the bowel was done in 1 case and panhysterectomy plus partial excision of the endometrioma was done in 1 case.

b. When the point of obstruction was in the distal portion of the ileum. Enterostomy plus ileal resection was done in 1 case. An initial Witzel ileostomy and a subsequent right hemicolectomy and ileotransversostomy were done in 1 case. Ileal resection plus ileocecostomy and removal of the remaining tube and ovary were done in 1 case.

These patients had been followed up by examination and letters for from 1 month to 21 years. An excellent result with complete relief of the symptoms was obtained in 12 cases, a good result in 2 cases, and a fair result in 2 cases.

There were no deaths.

[1]It is to be emphasized that most of the cases in the current series occurred before the time of the changing concept of treatment from that of resection of the bowel to that of bilateral oophorectomy. Present treatment consists in panhysterectomy plus conservative treatment of the bowel.

REPORT OF CASES

CASE 1. A single, white woman 43 years of age complained of symptoms fairly typical of partial obstruction of the small intestine of 2 months' duration. Physical examination revealed an emaciated weak woman who had abdominal distention and visible peristaltic waves. A roentgenogram of the colon was positive for obstruction of the small bowel. Medical treatment in the form of a double lumen tube, blood transfusions and supportive therapy was instituted. Complete obstruction occurred 1 week after admission. A Witzel type enterostomy was done and it was believed that ileocecal obstruction caused by a carcinoid existed. Four weeks later right colectomy was carried out with side-to-side ileocolostomy. No abnormality or endometriosis was found in the pelvis. Pathologic examination revealed that the obstruction was caused by a region of endometriosis in the terminal portion of the ileum (Fig. 1).

CASE 2. A white woman 33 years of age, who had been married for 9 years but had never been pregnant, complained of episodes of colicky lower abdominal pain of several months' duration. She had always been constipated. She suffered from severe acquired dysmenorrhea. Abdominopelvic examination showed tenderness and some rigidity in the right lower quadrant of the abdomen and an irregular, tender mass in the right adnexa. On abdominal exploration 3 small contracted and scarred regions were found in the terminal portion of the ileum. The middle region was producing partial obstruction of the terminal portion of the ileum. About 6 inches (15 cm.) of the ileum, including the three regions, was resected and an end-to-end anastomosis was made. The pathologist reported the process as one of multiple endometrioma of the ileum with partial intestinal obstruction. The patient made an uneventful recovery.

CASE 3. A white woman 32 years of age, married for 10 years but never pregnant, complained of symptoms fairly typical of partial colonic obstruction which were present for 10 days prior to each menstrual period. She stated that 2 years previously myomectomy and left oophorectomy had been performed. Nine months prior to admission the symptoms of obstruction had begun to increase in severity. For 2 months obstruction had been almost complete.

Physical examination revealed a thin, malnourished woman. Pelvic examination indicated the presence of a large mass, probably an ovarian cyst, in the right adnexa. Proctoscopic examination indicated this mass and the angulation of the bowel produced by it. Abdominal exploration was carried out for carcinoma of the sigmoid with obstruction. Because of the huge dilatation of the colon and

cecum proximal to the mass in the sigmoid and a large simple cyst of the right ovary cecostomy and right salpingo-oophorectomy were done. Three weeks later resection of 20 centimeters of sigmoid which contained the mass together with a portion of the posterior uterine wall was carried out and an end-to-end anastomosis was made. The patient made a good recovery. Pathologic examination showed complete sigmoidal obstruction by the endometrioma.

CASE 4. A white single woman 31 years of age, who had had 1 pregnancy which had ended in abortion, complained of intermittent pain in the right lower quadrant of the abdomen of 9 years' duration which occurred 1 week before, during and after menses. The pain had been progressively increasing in severity and for the past month had been persistent without relief. Previous surgical treatment included appendectomy done 9 years before and left radical and right simple mastectomy done 3 years before for bilateral intraductal papillary carcinoma.

Abdominal examination revealed in the region of the cecum a peculiar ovoid flat tumor which was movable and tender. On exploration of the abdomen a region of endometriosis was found to be partially obstructing the terminal portion of the ileum. Right salpingo-oophorectomy and resection of the terminal portion of the ileum with ileocecostomy and an end-to-side anastomosis were done. The patient made an uneventful recovery. The pathologist reported partial ileal obstruction by a region of infiltrating endometriosis.

CASE 5. A white married woman 54 years of age, who had been pregnant once and was 3 years past the menopause, complained of bleeding from the rectum and constipation—both of 18 months' duration. Other symptoms of which she complained were excessive gas and occasional pain in the left lower abdominal quadrant which were relieved by repeated enemas. Rectal examination disclosed a carcinoma on the posterior rectal wall and biopsy showed this to be an adenocarcinoma, grade 1 (Broders' method). A roentgenogram of the colon revealed a partially obstructing lesion high in the sigmoid with occasional diverticula below this point. The carcinoma of the rectum was treated with radium and the patient returned in 3 months for an abdominal exploration. Marked obstruction of the midsigmoid by a lesion that grossly resembled endometriosis was found. An area of the sigmoid including the lesion was removed by an exteriorization operation by the clamp method. One month later radical posterior resection was done for the removal of a recurring adenocarcinoma of the rectum. The patient's recovery was uneventful. Pathologic examination of the specimen showed an endometrioma of the sigmoid which had caused almost complete obstruction.

CASE 6. A white woman 45 years of age, who had had 1 child and was now separated from her husband, complained of severe lower abdominal cramping pain on the first 2 days of her period, a sense of pressure in the lower part of her abdomen and sacral backache—all of 5 months' duration. One year previously vaginal myomectomy, dilatation and curettage, and perineorrhaphy had been performed. Metrorrhagia had been present for 5 weeks.

Pelvic examination showed marked cervicitis and erosion and a suspicious "precancerous" region on the posterior lip of the cervix. On abdominal exploration a nodule in the sigmoid causing almost complete obstruction was found. A first stage Mikulicz operation and panhysterectomy plus appendectomy were performed. About 2 weeks later a second stage Mikulicz operation was done and the colonic stoma was closed 4 months later. Recovery was good. The pathologist reported sigmoidal obstruction caused by endometriosis.

CASE 7. A white single woman 46 years of age complained of dull pain across the lower part of the abdomen and severe "comenstrual" and moderate intermenstrual constipation of 5 years' duration. She stated that 5½ years previously subtotal hysterectomy and left salpingo-oophorectomy had been performed and 5 years previously colostomy had been performed to relieve an acute sigmoidal obstruction caused by what was believed to be a malignant lesion.

Sigmoidoscopic examination revealed marked narrowing of the lumen of the sigmoid. The mucosa was intact and the narrowing appeared to be due to an extrarectal mass. On exploration of the abdomen a strictured region just above the rectosigmoidal juncture was found. This region was resected and an end-to-end anastomosis was made over a rubber tube. Six months later the colonic stoma was closed. Pathologic examination of the specimen showed sigmoidal obstruction caused by an endometrioma.

CASE 8. A white woman 43 years of age, who had been married for 17 years without ever having become pregnant, complained of symptoms fairly typical of chronic intermittent partial intestinal obstruction of 11 years' duration. She stated that appendectomy had been done 21 years previously, partial hysterectomy and right salpingo-oophorectomy had been done 14 years previously, and hemorrhoidectomy 3 years previously.

Pelvic examination showed no uterine fundus and a fairly normal cervix. The roentgenogram of the colon showed a constriction high in a redundant sigmoid which was questionably caused by some extrinsic process. On abdominal exploration endometriosis was found involving the mesentery of the midsigmoid and almost completely encircling the intestinal lumen, causing marked constriction in this region. An exteriorization operation with removal of the lesion and left salpingo-oophorectomy was accomplished. The patient made an uneventful recovery. The pathologist reported sigmoidal obstruction caused by a region of endometriosis which had practically encircled the sigmoid, had deeply infiltrated the intestinal wall and had reduced the diameter of the lumen to 5 millimeters.

CASE 9. A white woman 41 years of age, who had been married for 12 years without becoming pregnant, complained of "comenstrual" constipation of 5 years' duration. Three weeks prior to admission she presented symptoms that were fairly characteristic of colonic obstruction. Physical examination revealed that the uterus was somewhat fixed in the midposition by a thickened mass in the region of the left broad ligament and by nodules in the pouch of Douglas which via the vaginal speculum appeared "blue-domed." A roentgenogram of the colon showed a lesion in the sigmoid which had completely obstructed the retrograde flow of barium. On abdominal exploration the pelvic mass was found to involve the posterior wall of the uterus and the sigmoid. Transverse colostomy was performed. One month later the lesion and a part of the midportion of the sigmoid were resected and an end-to-end anastomosis was made. The colonic stoma was closed later and a series of roentgen treatments over the adnexa was given to produce cessation of ovarian function. The patient made a good recovery. Pathologic examination showed sigmoidal obstruction caused by diffuse endometriosis of the sigmoid.

CASE 10. A single white woman 41 years of age complained of severe "comenstrual" constipation of 18 years' duration and of symptoms fairly typical of chronic intermittent partial intestinal obstruction for the last few years. She stated that appendectomy had been done 13 years previously and unilateral salpingo-oophorectomy 1 year previously.

Physical examination showed a slightly enlarged uterus with a pedunculated, egg-sized fibroid on its wall. Sigmoidoscopic examination revealed sharp anterior angulation of the bowel at 20 centimeters. A roentgenogram of the colon showed a long, constricting, obstructing lesion in the midsigmoid. The abdomen was explored and extraperitoneal resection of an endometrioma of the lower sigmoid was done with a catheter colostomy which was later closed. The patient made an uneventful recovery. The pathologist reported sigmoidal obstruction by a discrete endometrioma.

CASE 11. A white married woman 48 years of age, who had never been pregnant, complained of severe constipation and acquired menstrual pain. During menstruation she was obstipated for 1 or 2 days. Ten years previously she had undergone partial hysterectomy because of "tumors" and menorrhagia.

Physical examination revealed a hard mass filling the pouch of Douglas. Abdominal exploration was performed and, low down between the vaginal vault and the rectum, a hard mass suggesting an endometrioma and causing definite obstruction was found. A portion of the bowel was resected and an end-to-end anastomosis plus appendicostomy was done. The patient made an uneventful recovery. Pathologic examination of the specimen revealed obstruction by a large endometrioma.

CASE 12. A white woman 32 years of age, who had been married for 10 years without having become pregnant, complained of severe "comenstrual" constipation, rectal "soreness" and sacral pain. Physical examination revealed a slightly irregular mass in the posterior fornix between the rectum and the vagina measuring 4 by 4 centimeters and protruding into the rectum. Sigmoidoscopic examination showed an anterior extrarectal mass at about 10 centimeters above the anus. Abdominal exploration revealed an endometrioma on the anterior wall of the sigmoid with definite obstruction. The anterior wall of the sigmoid with the tumor was resected and the bowel was closed transversely. Myomectomy, appendectomy, and excision of other regions of endometriosis were accomplished. The patient made a good recovery. The pathologic specimen consisted of the resected endometrioma covered on one aspect by a layer of colonic mucosa.

CASE 13. A white married woman 45 years of age, who had never been pregnant, complained of "comenstrual" constipation and pain in the left lower quadrant of the abdomen of 4 years' duration. Nine months previously she had had symptoms fairly typical of acute intestinal obstruction and on abdominal exploration an obstructive lesion thought to be nonmalignant had been found in the rectosigmoidal region. Colostomy had been performed.

Physical examination revealed abdominal distention. A roentgenogram of the colon showed an irregular filling defect in the sigmoid near the colonic stoma. Sigmoidoscopic examination showed contraction of the bowel at 24 centimeters as if by external pressure. Abdominal exploration showed a pelvic mass involving one loop of small intestine and a portion of the sigmoid. The loop of small intestine was mobilized and the portion of sigmoid resected. An end-to-end anastomosis was made. The patient's recovery was satisfactory and the colonic stoma was closed 1 month later. The pathologist reported sigmoidal obstruction by an infiltrating region of endometriosis.

CASE 14. A white woman aged 31 years, who was separated from her husband and who had had 1 pregnancy 5 years previously, which had been terminated by a self-induced abortion, complained of 4 to 5 loose stools with slight bleeding per day for 2 days premenstrually, accompanied by intermittent cramping abdominal pain, and later postmenstrual constipation—all of 6 months' duration. She stated that 1 year after the aforementioned self-induced abortion dilatation and curettage had been performed because of menorrhagia, clots, and severe pelvic pain.

Physical examination demonstrated bilateral cystic adnexal masses and a firm mass in the pouch of Douglas which encroached on the anterior intestinal wall. Sigmoidoscopic examination showed adhesion of the anterior sigmoidal wall to an extrarectal mass, angulation of the bowel to the left, and marked luminal obstruction—all consistent with endometriosis. A roentgenogram of the colon showed fixation of the lower part of the sigmoid and luminal narrowing by an extrinsic process consistent

with endometriosis. Abdominal exploration revealed that the endometriosis was almost completely kinking the sigmoid and had attached it to the back of the cervix. Panhysterectomy, appendectomy, and biopsy of the endometrioma of the sigmoid were performed. Recovery was uneventful. The pathologist reported endometriosis of the sigmoid, extensive endometriosis of the posterior surface of the uterus, and bilateral chocolate ovarian cysts.

CASE 15. A white married woman 32 years of age, who had never been pregnant, had previously complained of severe "comenstrual" constipation and rectal pain. She stated that 2 years previously the left tube and ovary had been removed because of pain in the left lower abdominal quadrant. Five months previously symptoms consistent with complete colonic obstruction had developed. On exploration of the abdomen what was thought to be a malignant lesion had been found to be obstructing the lower part of the sigmoid. Colostomy had been performed.

Physical examination on admission showed nodularity of the uterosacral ligaments and an extrarectal mass behind and to the left of the cervix. Sigmoidoscopic examination revealed an anterior extrarectal mass at 18 centimeters which impinged on the lumen of the bowel. On abdominal exploration an endometrioma of the sigmoid, which had caused obstruction, was found. The involved portion of the sigmoid was firmly adherent to the cervix. The uterus, right tube and ovary, and the portion of the sigmoid including the lesion were removed. End-to-end anastomosis was performed and also appendicostomy. The colonic stoma was closed 7 months later. The pathologist reported that in the resected portion of the sigmoid there was a region of endometriosis 4 by 3 by 2 centimeters infiltrating into the sigmoidal wall and causing obstruction.

CASE 16. A white married woman 35 years of age, who had never been pregnant, complained of diarrhea, gas, and abdominal colicky pain which were present on the first few days of menstruation. Ten months previously the patient had had an acute episode of lower abdominal colicky pain with vomiting and no bowel movement for 3 days. Previous surgical treatment had consisted of appendectomy done elsewhere and curettage done as a sterility study measure 1 year before.

Physical examination revealed an extrarectal nodular mass about 2 centimeters in diameter on the anterior rectal wall. Sigmoidoscopic examination showed at about 12 centimeters up on the anterior rectal wall an impinging region of induration about the size of a 5 cent piece and a roentgenogram of the colon showed a deformity of the sigmoid. Exploration of the abdomen showed that an endometrioma measuring about 1½ inches (4 cm.) in diameter and situated at the bottom of the pouch of Douglas was causing almost complete obstruction of the sigmoid. A segment of the sigmoid containing the endometrioma was resected and an end-to-side anastomosis was established. The patient made an uneventful recovery. Pathologic examination of the specimen showed the sigmoid doubled on itself with a large endometrioma in its midportion (Fig. 2). The obstruction had been caused by infiltration of the mass into the sigmoidal wall and compression of the sigmoid by the mass.

PATHOLOGIC OBSERVATIONS

Pertinent gross pathologic observations noted on the 15 resected lesions and the 1 partially excised lesion were as follows:

Nature. Three sigmoidal lesions had produced obstruction by virtue of an annular or napkin-ring type of infiltration with more or less concentric narrowing of the intestinal lumen. In 8 additional cases (2 lesions classified as high rectal and 6 as sigmoidal) the appearance was that of polypoid submucosal infiltration producing obturation of the intestinal lumen. In 2 other instances an eccentric cicatrization produced by infiltrating endometriomas had produced acute angulation while at the same time submucosal proliferation of the endometrial tissue gave a superadded factor of obturation. A combination of impingement and kinking from endometrial adhesions obtained in the 3 cases of ileal endometrioma with obstruction.

Size. Gross limits of the infiltrations varied from 6 by 4 by 2.5 centimeters to 1 by 1 by 1 centimeters. The average dimensions were 2.5 centimeters in diameter with 7 of the endometriomas exceeding this size.

Color. The dark red mottled appearance so characteristic of the lesions as seen at operation was replaced in the formalinized specimens by the presence on the peritoneal and cut surfaces of scattered bluish black spots on a whitish brown background of fibromuscular tissue. Some of the cut surfaces presented a striated appearance and from them tiny drops of brownish black fluid could be expressed by scraping with a knife.

Consistency, mucosal-serosal relations, and so forth. The involved tissues were nodular, firm, and fibrous without sharp delineation in the zones demarcating the edges of the infiltrations. In 9 instances the overlying mucosa was puckered in a roset fashion, in 6 it was irregularly pitted and in 1 case it presented an edematous polypoid appearance. Although no gross mucosal ulceration was noted, in 11

TABLE I.—POSITION OF THE ENDOMETRIAL GLANDS AND STROMA IN ENDOMETRIOMA OF THE BOWEL FROM THE CURRENT SERIES

Case	Segment of bowel	Submucosa		Muscularis		Serosa	
		Glands	Stroma	Glands	Stroma	Glands	Stroma
1	Ileum	+*	+	+	+	+	+
2	Ileum	0	0	+	+	+	+
3	Sigmoid	+	+	+	+	0	0
4	Ileum	0	0	+	+	+	+
5	Sigmoid	+	+	+	+	0	0
6	Sigmoid	0	0	+	+	0	0
7	Sigmoid	0	0	+	+	0	0
8	Sigmoid	+	+	+	+	+	+
9	Sigmoid	+	+	+	+	0	0
10	Sigmoid	+	+	+	+	+	+
11	Rectosigmoid	+	+	+	+	+	+
12	Rectosigmoid	+	+	+	+	+	+
13	Sigmoid	+	+	+	+	+	+
14	Sigmoid (excision)	−	−	+	+	+	+
15	Rectosigmoid	+	+	+	+	+	+
16	Sigmoid	+	+	+	+	+	+

*+=positive; 0=negative; −=not stated.

of the 16 cases the mucosa was more or less firmly adherent to the underlying submucosa and to the muscularis propria. Irregular puckering of the peritoneal coat was noted in all of the lesions.

Proximal segments. In all of the specimens in which accurate luminal dimensions could be studied the bowel proximal to the obstruction showed the effects of stasis in the form of dilatation (Fig. 1). In 11 cases this degree of dilatation was estimated to be two or more times the luminal diameters distal to the endometriomas. This obstructive dilatation, moreover, was paralleled in a general way by increases in thickness of the muscularis propria. In 9 of the specimens this layer was approximately doubled in thickness.

Associated pathologic conditions. Uterine fibromyomas had been noted at operation or removed in 8 of the 16 cases. Six patients had extensive ovarian endometriosis with tarry cysts. Four patients had simple ovarian cysts and the ovaries and tubes of an additional 2 were involved in adhesions. If in addition we consider that 9 patients had previously undergone surgical exploration of the pelvis it becomes apparent that the obstruction of the bowel by endometriosis was but a part of the picture.

MICROSCOPIC FEATURES

In essence the intestinal lesions consisted in invasion by endometrial glands and stroma of the serosa, muscularis, submucosa, and mucosa in variable combinations (Table I). Added to this was the important factor of reactive fibrosis with stenosis resulting from the contraction of maturing fibrous tissue. Since the process was fundamentally extrinsic in point of origin, mucosal changes were the least frequently noted. In 4 instances the endometrial glands and stroma invaded the muscularis mucosae and in 1 of these a microscopic-sized area of ulceration involved the overlying epithelium. Considerable mucosal scarring was present. Infiltration of the submucosa obtained in 11 instances (Fig. 3). All specimens showed infiltration of the muscularis propria. All 3 specimens of ileal endometriosis showed a major concentration of endometrial glands and stroma in the serosal and outer muscular coats. In contrast the sigmoidal and high rectal lesions were generally of the "deep" type—that is, the inner circular layer of muscle and the submucosa exhibited the greatest number of these ectopic elements. As a matter of fact in 5 cases of well circumscribed endometriosis of the sigmoid routine sections failed to reveal the presence of serosal endometriosis, although one certainly might concede that it had existed earlier in the course of the invasive process.

Although the proportion of endometrial glands to stroma varied a great deal (Fig. 3), in general these elements were present in about equal proportions. The glandular and stromal elements were in all cases similar to their normal intrauterine counterparts and they exhibited pictures typifying all the phases of the menstrual cycle. Within the musculature of the bowel the endometrial glands seemed to proliferate in an axis parallel to that of the muscle bundles (Fig. 4) as though the invading tissue were following the lines of least resistance rather than permeat-

Fig. 1. Gross specimen (Case 1) of terminal ileum, cecum, appendix, and ascending colon. Note endometriosis causing obstruction at a point 5 centimeters proximal to the ileocecal valve and the dilatation of the bowel above this point.

Fig. 2. Gross specimen (Case 16) of sigmoid which is doubled on itself. Note the large endometrioma (5 by 5 by 3 cm.) in its midportion which has impinged on the intestinal lumen to obstruct it.

ing lymphatic spaces. The presence in 6 cases of cystic glandular hyperplasia was correlated with a clinical history of menstrual irregularity noted in the histories.

Studies made using the van Gieson stain for fibrous tissue revealed in all instances fibroblasts and collagenous fibrils around the nests of endometrial glands and stroma (Fig. 5). This fibrous tissue was occasionally hyalinized. In both the fibrous and the hyalinized examples this reaction tissue was seen to infiltrate the invading glands and stroma on the one hand and the invaded muscular tissues on the other.

Stains for iron demonstrated the presence of this substance in 5 instances only. This was something of a surprise since we had surmised that the cicatrization would obtain on the basis of a reaction to hemosiderin deposited during "menstruation" from the ectopic endometrium.

COMMENT

Endometriosis is the only common condition in which there occurs invasion of one tissue by another normal tissue of the same host.[1,2] When the bowel is the victim of this infiltrative process the segments affected are usually those which are situated in the pelvis. These are the sigmoid, the rectosigmoidal juncture, the rectum, and the distal portion of the ileum. As with endometriosis elsewhere the survival of the lesions is predicated on the influence of the cyclic hormonal stimulation of the ovaries. In the absence of this stimulation endometriosis undergoes retrogression. Endometriosis invades the intestinal wall from its serosal side and grows inward into the muscular layers and the submucosa (Fig. 6). Rarely may the mucosa of the bowel be invaded grossly (Fig. 7).

Sampson's implantation hypothesis plus Harbitz' idea of "extraperitonealization" will explain the pathogenesis of endometrioma of the sigmoid and ileum, while an equally good alternative hypothesis is that of lymphatic and venous metastasis (7, 31).

The frequency with which the diagnosis of endometriosis (35) is made by the clinician, the surgeon or the pathologist varies with their "threshold of suspicion" and it is our feeling that many cases have passed unrecog-

[1]Traumatic rupture of the spleen is occasionally followed by a peritoneal seeding of splenic transplants.

[2]The placenta might be considered to be an exception, depending on the interpretation of the word "host."

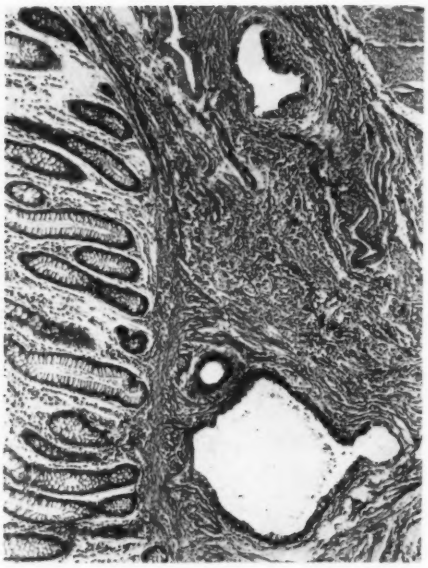

Fig. 3. Sigmoid (Case 3). Endometrial glands and stroma are seen in the submucosa. Note variation between amount of glands and stroma present (hematoxylin and eosin ×57).

Fig. 4. Sigmoid (Case 3). Note that the long axis of the muscle fibers runs parallel to the long axis of the endometrial glands (hematoxylin and eosin ×31).

Fig. 5. Sigmoid (Case 3). Note the endometrial glands in the inner muscular layer with fibrosis around them (van Gieson ×88).

nized. The truth of this statement is also applicable to the complication of intestinal obstruction caused by endometriosis since against our series of 16 cases a "literature" of only 40 cases seems inadequate.

The symptoms of intestinal obstruction caused by endometriosis may be divided into two main groups: (1) the symptoms and signs of usually extensive pelvic endometriosis and (2) the symptoms and signs of intestinal obstruction in its various degrees.

Endometriosis occurs in women usually between the ages of 30 and 50 years. The majority of the women are sterile. More than half of the women have never been pregnant[1] and at least two-thirds have never carried a fetus through to full term delivery.

A periodicity of symptoms associated with the menstrual cycle and the onset of menstruation is the single most important sign of endometriosis *per se* and its complication of intestinal involvement. This periodicity of symptoms includes both the symptoms of

[1]This too may depend on the physician's "threshold of suspicion" in the search of the patient's past history.

Fig. 6. Sigmoid (Case 5). Endometrial glands and stroma are seen in the submucosa. Of significance is the fusion in a scarred area of the muscularis mucosae and propria (hematoxylin and eosin ×70).

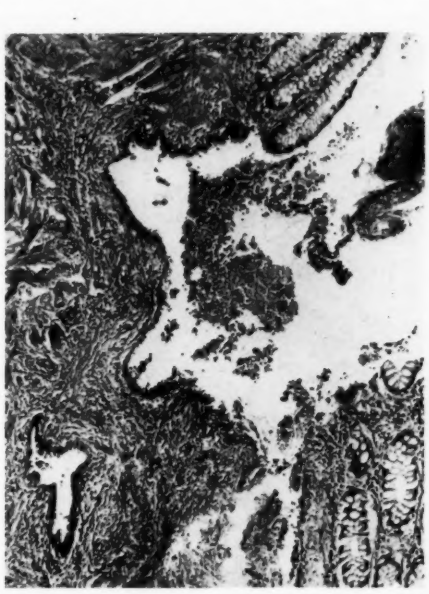

Fig. 7. Sigmoid (Case 8). Note ulceration of the mucosa (rare and not characteristic) and the presence of endometrial glands and stroma. The muscularis mucosae is thickened and fibrosed (hematoxylin and eosin ×70).

endometriosis and those of intestinal obstruction. A history of the symptoms of acquired dysmenorrhea, rectal pain associated with or between defecations, sacral pain, or deep pelvic pain or discomfort (which may extend down into the thighs and is made worse by jarring), severe constipation or diarrhea, and dyspareunia that are increased just before, during, or just after menstruation is usually indicative of extensive endometrial involvement of the sigmoid, rectosigmoidal juncture, or rectum. When these symptoms become progressively worse and lengthen out in duration premenstrually, postmenstrually, or both, obstructive intestinal symptoms are usually imminent.

The symptoms of intestinal obstruction then become superimposed on those of endometriosis of the bowel, at first usually only "comenstrually." These symptoms for the sigmoid and below are those of lower abdominal pain (which is one of the first to be present), along with abdominal distention, and finally obstipation, which may be present for only 1 or 2 days during the period. When the sigmoid or more distal portions of the bowel are obstructed, nausea and vomiting usually occur late because of the competence of the ileocecal valve (45). Occasionally a reflex type of nausea and vomiting may be encountered. The symptoms of the endometriosis plus the superimposed symptoms of the intestinal obstruction, which at first are mild, become progressively worse, lengthen out premenstrually or postmenstrually, and either go on to the production of acute complete or partial obstruction at one of the menstrual periods or assume the form of chronic intermittent partial obstruction of high or low grade.

Compared with intestinal obstruction in general caused by endometriosis ileal obstruction caused by endometriosis more often occurs among younger women, who usually have less extensive pelvic involvement by endometriosis or sometimes no other grossly visible pelvic involvement. These patients may or may not have the general symptoms of endometriosis, but when these symptoms are

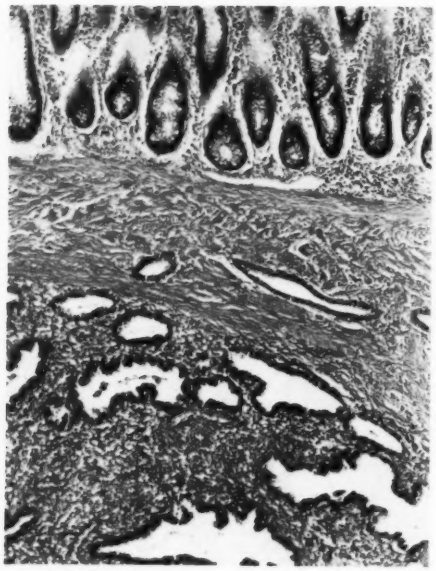

Fig. 8. Sigmoid (Case 11). Note the island of endometrial glands and stroma in the late differentiative phase in the submucosa (hematoxylin and eosin ×66).

present it is usually to a lesser degree. This is represented by the facts that the group with ileal involvement had a higher fertility rate, fewer previous pelvic operations, fewer uterine fibroids and a lesser incidence of associated pelvic pathologic changes. Also in the ileal group no patient had rectal pain, constipation was less frequent, only 1 patient complained of diarrhea and no patient had blood in the stools. Vomiting was a more frequent symptom than obstipation.

Often, according to the literature, and once in the current series, obstruction of the distal portion of the ileum by endometriosis has been diagnosed clinically as appendicitis accompanied by paralytic ileus. If, however, the history is taken carefully, the symptoms of the endometriosis are usually elicited. Definite symptoms of low ileal obstruction are superimposed on the periodic "comenstrual" symptoms of acquired dysmenorrhea, constipation, and so forth.

Gross blood in the stools is usually not an important symptom of endometriosis of the bowel. It is of significance only when other anorectal lesions have been excluded and when it is present only at the menstrual period.

Valuable adjuncts to the symptoms in the diagnosis of intestinal obstruction as caused by endometriosis are digital examination of the vagina and rectum, the sigmoidoscopic and roentgenographic examination of the colon and the terminal portion of the ileum after administration of a barium enema.

Pelvic examination most often reveals tender palpable nodules in the rectovaginal septum or the pouch of Douglas, frequently the presence of associated uterine fibroids and in many cases the presence of ovarian cysts, usually bilateral. On operation these are most often observed to be the chocolate cysts of endometriosis. Pelvic examination is best made just before or during menstruation because of increased tenderness and congestion. If a discrete endometrioma is present in the rectovaginal septum it may be palpated. A thorough search of the vaginal vault via a speculum at the time of menstruation may reveal the presence of the purplish pink lesions of endometriosis which have invaded the vaginal wall. The vaginal wall may sometimes be invaded but the rectal mucosa almost never is.

On sigmoidoscopic examination there is rarely gross bleeding and almost never gross ulceration. The positive findings will be those of a greatly narrowed lumen, an anterior extrarectal mass, acute angulation of the bowel and mucosal puckering and congestion. The appearance is much like that of obstructing diverticulitis and cannot be positively differentiated from it by means of the sigmoidoscope but the intact mucosa differentiates it from carcinoma. Biopsy of the intestinal mucosa is usually not practical, for, since the mucosa is not extensively involved, the report will usually come back "negative" or "inflammatory change only." Even in the few cases in which rectal bleeding has been a symptom, the mucosa has appeared only puckered or adherent, but not ulcerated, and fairly normal. It is important to remember that carcinoma invades the intestinal wall from the mucosa outward while endometriosis invades it from the serosa inward.

A roentgenologic examination of the colon is assuming a rôle of importance in the diagnosis of endometriosis causing intestinal obstruction. If the obstruction is complete the employment of a roentgenogram of the colon may accurately localize the lesion. If the obstruction is incomplete the proper interpretation of the roentgenogram of the colon may not only localize the obstructing lesion but identify the cause as endometriosis as well. The characteristic lesion on roentgenologic examination of the colon is said to be a long, inconstant filling defect with sharp regular borders, intact mucosa and fixation of the bowel, which is very tender to palpation.

Diagnosis. The diagnosis of intestinal obstruction which has been caused by endometriosis or endometrioma may best be made by first obtaining an accurate history of the development of the symptoms which are diagnostic of endometriosis. Points of importance are as follows: (1) a woman in the reproductive period of life, usually between the ages of 30 and 50 years, (2) who is in fairly good general health and has not lost weight, (3) who suffers from absolute, relative, or secondary sterility or who has married late or has not been pregnant for some time, (4) who has acquired dysmenorrhea, and (5) who has a history of usually a year or longer of symptoms which occur with menstrual periodicity; (6) symptoms, such as severe constipation, "rectalgia" or dyschezia, dyspareunia, occasionally diarrhea, and rarely rectal bleeding; (7) low deep pelvic discomfort caused by jarring of the body; (8) sacral backache which may run down into the thigh; and (9) symptoms of intestinal obstruction such as lower abdominal cramping colicky pain, abdominal distention, and obstipation or vomiting or both which have shown menstrual periodicity and become progressively more severe.

These symptoms plus the finding of: (1) on pelvic examination tender nodules in the pouch of Douglas or a large tumor of the rectovaginal septum and associated uterine fibroids and bilateral ovarian cysts, and (2) a sigmoidoscopic examination that shows an intact puckered mucosa and a stenosed or narrowed intestinal lumen from an extrarectal mass, or (3) a roentgenogram of the colon that shows a long, inconstant filling defect with regular borders, intact mucosa and fixation of a tender bowel indicate a highly presumptive diagnosis of intestinal obstruction caused by endometriosis. Positive diagnosis can be made only by operation and surgical biopsy of the lesion with frozen section and microscopic pathologic confirmation.

Fig. 9. Sigmoid (Case 16). Note the large cyst in the submucosa and the invasion of the submucosa and muscular layers by endometrial glands and stroma in the late differentiative phase (hematoxylin and eosin ×9).

Treatment. 1. Surgical treatment.—The treatment of intestinal obstruction caused by endometriosis is surgical. The basic principle in the treatment of this condition is the fact that retrogression of endometriosis depends on the absence of ovarian hormonal stimulation. Hence, to treat the patient the surgeon may elect usually to remove both ovaries[1] (as pointed out by Milnor and others) or occasionally to resect the bowel (30) or in rare instances to do both. Factors to be considered by the surgeon are the age of the patient, her desire to become pregnant, the probability of

[1]Radiation castration could not be expected to produce rapid regression of the obstructing intestinal lesion. Surgical castration alone on the other hand is often followed promptly by a "relenting" of serious obstructive symptoms.

her becoming pregnant, the existence of associated pelvic pathologic lesions, and the location and extent of the endometriosis together with the degree of intestinal obstruction present. Decision to do a conservative operation implies that the surgeon must be sure that the intestinal lesion is *not* in fact a carcinoma.[1] Because the treatment of intestinal obstruction varies with the location of the lesion the therapy of colonic obstruction will be discussed first followed by that of ileal obstruction.

a. Treatment when the point of obstruction is in the sigmoid, rectosigmoidal junction or rectum.—In these cases the involvement of the pelvis and colon by endometriosis is usually extensive and bilateral oophorectomy or panhysterectomy is usually indicated. Panhysterectomy is justified because the endometrioma of the colon will retrogress, the obstruction will be relieved and associated pelvic lesions, which are nearly always present, will be removed. If the obstruction is complete or incomplete with much dilatation of the proximal portion of the bowel, temporary proximal colostomy should also be done to decompress the bowel. The stoma may be closed in a few months after subsidence of the endometrioma. If the patient is a young woman who is desirous of a pregnancy and whose pelvic organs are essentially normal, resection of the involved segment of the bowel is the procedure of choice.

b. Treatment when the point of obstruction is in the ileum.—In these cases the treatment of choice is resection of the bowel; or, if the diagnosis is apparent to the surgeon, a short-circuiting procedure. The obstruction in these cases is to some degree caused by the partial occlusion of the lumen by the endometrioma but more by the tough dense adhesions of endometriosis and resultant kinking of the bowel.

2. Surgical treatment versus roentgen therapy. — Roentgen therapy should be reserved for those patients who are extremely poor operative risks or who have had intestinal recurrence of endometriosis following operations in which conservative treatment was given to the ovaries.

[1]Chiefly among cases found early in our series, the surgeon felt reasonably certain that the intestinal lesion was malignant.

Presumable relationship of endometriosis to carcinoma. The question whether carcinoma may develop from endometriosis or on the basis of it has been much debated (9, 42). It is our conclusion that a presumable relationship may exist but there is no definite factual proof of it.

SUMMARY AND CONCLUSIONS

1. An analytic study of clinical data on 16 from the current series of cases of intestinal obstruction caused by endometriosis has been presented as well as the results of a pathologic study of these cases.

2. To make the diagnosis of endometriosis as a cause of intestinal obstruction, the possibility of its occurrence should be kept in mind in every case of intestinal obstruction in which the patient is a woman from 30 to 50 years of age. Acquired dysmenorrhea, menstrual periodicity of symptoms, sterility, rectal or pelvic pain, absence of loss of weight, the presence of associated uterine fibroids or ovarian cysts, and a long history of intestinal symptoms which suggest progressive intestinal obstruction with frequent exacerbations at menstruation are most important points in the diagnosis of this condition.

3. Severe constipation, lower abdominal pain and distention are almost always present. If the obstruction is ileal, vomiting is almost always present, while if the obstruction is colonic, obstipation is more often present. Diarrhea is occasionally a symptom but the presence of gross blood in the stool in the absence of other anorectal disorders is very infrequent. If present at the time of menstruation it is of significance.

4. The symptoms of menorrhagia and metrorrhagia are not the symptoms of endometriosis *per se* but rather the symptoms of associated pelvic pathologic lesions.

5. An accurate preoperative diagnosis of intestinal obstruction caused by endometriosis can usually be made on the basis of the clinical history, digital examination, sigmoidoscopic examination, and careful interpretation of the roentgenogram of the colon and the terminal portion of the ileum. The finding of a firm tumor in the rectovaginal septum or of tender palpable nodules plus the

palpation of uterine fibroids and bilateral ovarian cysts is suggestive of endometriosis as the cause when intestinal obstruction is present. Sigmoidoscopic examination, with the presence of an extrarectal mass and an intact puckered mucosa, and a roentgenogram of the colon, with the presence of a long, inconstant filling defect with sharp regular borders and an intact mucosa, are the two most valuable adjuncts to diagnosis when the lesion is in the lower bowel.

6. Surgical biopsy of tissue from the vaginal vault, if the endometrioma is in the rectovaginal septum and has invaded the vaginal mucosa, may afford pathologic confirmation of the clinical diagnosis but biopsy of the rectal mucosa is usually noninformative, as the tissue in all the cases in which this was done in the current series was reported as inflammatory.

7. Obstruction of the ileum as caused by endometriosis presents a less characteristic clinical picture than that in the sigmoid or below.

8. The treatment of intestinal obstruction caused by endometriosis is surgical. A preoperative diagnosis of endometriosis as a cause of colonic obstruction will obviate the necessity for resection of the bowel in most instances and surgical treatment will consist usually of bilateral oophorectomy or of panhysterectomy with or without temporary colostomy as is deemed necessary. The procedure of choice in obstruction of the ileum caused by endometriosis is ileal resection with or without preliminary enterostomy and with or without panhysterectomy as indicated by the presence and degree of associated pelvic pathologic lesions.

9. The mechanism of ileal obstruction was usually due to kinking caused by the endometriosis, while the obstruction in the sigmoid and below was more often due to an impingement of the endometrioma into the intestinal lumen.

10. If the patient is a young woman who has a discrete endometrioma of the ileum or sigmoid causing intestinal obstruction, if the pelvic organs are essentially normal to the extent that there appears to be a reasonable chance of an ensuing pregnancy and if the absence of menorrhagia or cystic endometrium has indicated evidence of fair ovarian function, a conservative operation should be done as regards the ovaries and a radical operation done as regards the obstructed bowel. Intestinal resection without oophorectomy is indicated.

11. Microscopically, endometrial glands and stroma were found in all layers of the intestinal wall (Figs. 8 and 9). They seemed to be most diffusely dispersed in the muscular layers. The endometriomas of the sigmoid were of the discrete or deep type, while the endometriomas of the ileum were located closer to the serosa.

12. Gross blood had been present in the stools of only 3 of 16 patients. The intestinal mucosa on gross inspection was intact in all cases but on microscopic examination it was invaded by endometriosis in 2 cases. In 1 of these cases microscopic ulceration had occurred.

13. Fibrosis around the endometrial glands and stroma was characteristic in all of the sections but a positive iron stain representative of hemosiderin was not characteristic. The muscle fibers in most instances seemed to run in the same long axis as that of the endometrial glands.

14. A plea is made for biopsy, frozen section, and pathologic confirmation of the clinical diagnosis in all cases of endometrioma obstructing the bowel, as carcinoma can be positively excluded only by this method. The prognosis of patients who have had intestinal obstruction caused by endometriosis is excellent and the surgical mortality rate was nil in the current series.

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FRACTURES OF THE TIBIAL CONDYLES INVOLVING THE KNEE JOINT

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An increasing agreement prevails among bone and joint surgeons that fractures involving joints, especially weight-bearing joints, should be restored to normal anatomical relationship as accurately as possible, and if necessary, by surgical measures. This viewpoint applies particularly to fractures of the tibial condyles involving the knee joint. There are some authors who believe that for the most part these fractures can be handled reasonably satisfactorily by manipulative measures. Watson-Jones would operate upon only the severely displaced condyles and would treat the majority of these fractures by manipulation. He has emphasized the likelihood of a poor result following any form of treatment of many of the badly comminuted fractures of the tibial condyles. E. M. Bick reported good functional results in 61 cases following nonoperative treatment. The majority of writers, however, Foged, Leadbetter and Hand, Buckner, Ronald, Palmer, Barr, and Knight, believe that the fractures of the tibial condyles with any degree of displacement, particularly the "bumper" fracture of the lateral tibial condyle, are best treated by open reduction and internal fixation.

At the Massachusetts General Hospital from which this series of cases is reported, we believe that, like any other type of fracture, each fracture must be evaluated as an entity and treated accordingly. Those fractures with little or no displacement can usually be handled by conservative measures, namely, manipulation followed by fixation or traction, while many of those with gross displacement and separation and depression of the tibial condyles had best be operated upon, but only by a skilled surgeon trained in meticulous joint surgery.

The commonest, most difficult to handle, and consequently the most important fracture involving the tibial condyles is the "bumper" or "fender" fracture which produces major damage to the lateral tibial table with or without damage to the external semilunar cartilage, the internal lateral ligament, and the cruciate ligaments (Fig. 1). This fracture is practically always sustained by a force which sharply adducts and flexes the knee, and in so doing, compresses the external semilunar cartilage, strains or tears the internal lateral ligament or the cruciate ligaments or both, and at the same time, depending on the severity of the force, impacts the lateral femoral condyle against the lateral tibial condyle, producing a compression fracture of the lateral tibial condyle which, in many cases, is severely comminuted. The maximum compression of the tibial condyle may be posterior to the midline because the most prominent curve of the femoral condyle occurs at this point.

In our cases the following were some of the causes of this type of fracture: a blow by the bumper or fender of an automobile on the outer side of the knee, a fall from a ladder landing with the knee flexed and adducted, a blow on outer side of the knee from a charging steer in one case, a large dog in another. In all, adduction and flexion of the knee were involved and in all cases too there were varying degrees of injury and subsequent reaction in the joint.

While fracture of the lateral condyle is the commonest injury involving the tibial condyles, others may occur, depending upon the mechanism of injury. If the blow is received on the inner side of the knee, fracture of the mesial tibial condyle may occur with injury to the internal semilunar cartilage and to the external collateral ligament of the knee, as occurred in the following case: a young man of 21, while attempting to bulldog a steer, was apparently struck on the inner aspect of the knee. There was immediate pain and disability and when the patient was seen 5 days later, roentgenograms revealed a separation and de-

Fig. 1. Mechanism of injury in various types of tibial table fractures. 1, Flexion and adduction of knee—strain of internal lateral ligament and compression of external semilunar cartilage. 2 and 3, Flexion and adduction of knee—injury to internal lateral ligament and probably cruciate ligaments with compression of external semilunar cartilage and comminuted fracture of the lateral tibial condyle. 4, In addition to injuries in 1, 2, and 3, there is also fracture of the fibula head. 5 and 6, Bursting fracture of both condyles, usually sustained by fall from a height. 7 and 8, Flexion and abduction of knee—injury to external lateral ligament and probably cruciate ligaments—also injury to internal semilunar cartilage and comminuted fractures of internal tibial condyle.

pression of the medial tibial condyle. No attempt was made to manipulate this fracture, but 7 days after injury, the internal tibial condyle was replaced to its normal position and held with a tibial bolt. The end-result was a knee which allowed the patient to drive an ambulance during most of the war. The knee was stable, had good alignment, with complete extension and flexion to 100 degrees.

Bursting fractures of both condyles may occur from very severe trauma either from a heavy blow or from falls from a great height. It is questionable whether this type of severely comminuted fracture can be sufficiently restored to justify open operation, and our belief is that these markedly comminuted ones possibly should be treated with gentle manipulation attempting to compress the fragments into more normal alignment with the hands of the operator, or by specially devised clamps. Such compression clamps cannot be used without danger, and not infrequently when operating upon tibial table fractures which have been unsuccessfully treated by using the clamp, we have found that more comminution of the fracture has been produced and fragments of articular cartilage and semilunar cartilage had been compressed further into the tibial head. If manipulation and compression are used, they should be followed by skeletal traction in the form of a Kirschner wire through the os calcis or lower end of tibia (Fig. 2). No matter what treatment is applied to these severely comminuted fractures, it is like-

Fig. 2. Anteroposterior and lateral views before and after treatment of a bursting fracture involving both tibial condyles and the upper tibial shaft. This type of fracture is best treated by gentle molding with the hands of the operator and skeletal traction (Kirschner wire through os calcis) for 6 or 8 weeks followed by immobilization in plaster for 6 weeks and walking with crutches for 4 or 5 months after injury. Open reduction is contraindicated.

ly that some patients will eventually develop extensive traumatic changes resulting in arthritis of varying degrees; in such cases the wearing of permanent external support or an arthrodesis of the knee are probabilities.

In discussing pathological findings, symptoms and signs, and x-ray findings, we shall describe particularly the "bumper" fracture because it is the classical fracture involving the tibial condyles.

PATHOLOGICAL FINDINGS

There is immediate swelling of the joint due to hemorrhage and increased synovial fluid. Fat droplets will be present in the fluid if the fracture involves the subchondral area. The swelling will increase for 24 or 48 hours. There is always more or less damage to the internal lateral and cruciate ligaments, and compression, usually, of the lateral tibial table, and not infrequently also, the fibular head. The degree of comminution, depression, and separation of the fragments varies. More often than not the lateral semilunar cartilage is injured and may be displaced downward into the spongy bone of the main fracture line along with fragments of the articular cartilage of the central portion of the lateral condyle. In the most severe cases actual subluxation of the knee joint due to the extensive ligamentous injury may be present.

SYMPTOMS AND SIGNS

Pain is most marked on the inner aspect of the knee due to the unusually severe injury to the internal lateral ligament chiefly at its femoral attachment. If the degree of fracture is not great, the patient may walk with assistance, but if the depression of the lateral condyle is marked, there will be complete disability; the knee will be held in a position of protection of 25 to 50 degrees of flexion and more or less "knock knee" position, depending upon the degree of depression of the lateral tibial condyle. All active and passive motions will be severely painful and palpation will reveal marked joint line tenderness and particularly severe at the femoral attachment of the internal lateral ligament. Damage to the popliteal structures and the peroneal nerve is rare but should always be suspected.

X-RAY STUDIES

Roentgenograms of both knees should be taken in the same relative position with anteroposterior, lateral, and oblique views. If the injured knee is held in a position of flexion, the normal knee should be roentgenographed in the same position. Little knowledge is gained from the lateral views, while the anteroposterior and oblique views will reveal the diagnosis. Because of the soft tissue swelling,

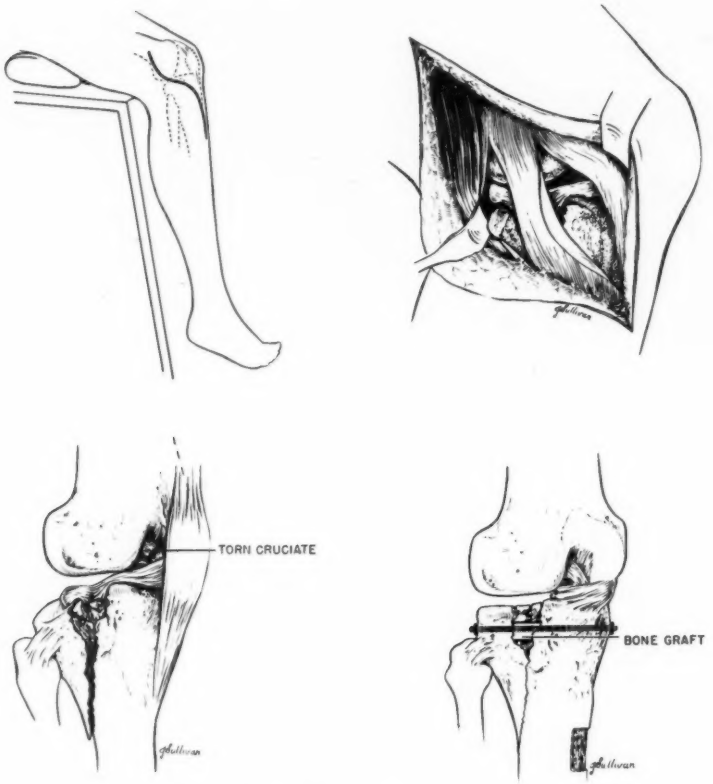

Fig. 3. Technique of operation.

more than the usual x-ray penetration should be used to demonstrate the fracture lines.

TREATMENT

For the severely depressed fracture of the lateral condyle, it is difficult for us to see how such a fracture can be replaced by manipulative means with any degree of accuracy. Therefore, we usually employ the following operation (Fig. 3). The lateral aspect of the knee is exposed with a bayonet incision, beginning just posterior to the lateral femoral epicondyle about 3 inches above the joint line and curving forward at the joint line, and down along the lateral portion of the tibial crest for 4 inches. The joint is opened anterior to the external lateral ligament with a curved incision and posterior to the ligament and popliteus tendon with a perpendicular incision. The upper tibia is exposed subperiosteally back to the tibiofibular ligament. Usually the semilunar cartilage is displaced downward into the fracture line, and therefore it must be removed in order to visualize the fracture and also to effect reduction. The displaced lateral portion of the tibial table is osteotomized and turned outward, and the depressed fragments elevated to their normal position. It may be necessary to remove some of the small fragments of articular cartilage which have little chance of survival. The main lateral fragment or fragments are then apposed to the tibia and secured by a long bolt with a tap on the inner end to maintain reduction. We must admit

Fig. 4. Preoperative and postoperative views of a typical "bumper" or depressed fracture of the lateral tibial condyle. The external semilunar cartilage which was depressed into the main fracture line was removed, the depressed "central" fragments were elevated and held in position with a graft which was taken from the lateral tibial crest, and the fractures were stabilized with a bolt and screw.

that extensive comminution of the fracture makes the procedure difficult. If this is the case, a tibial bone graft removed from the anterior portion may be driven under the joint surface to preserve the tibial plateau (Fig. 4). We have not found it necessary to suture any of the internal lateral ligaments, nor would we advise attempting to repair damaged cruciate ligaments at the time of reduction of the fracture. In only one case in our series was there severe damage to the cruciate ligaments which resulted in luxation of the knee, and a poor functional result was obtained because of instability of the joint in spite of the fact that the fracture was well reduced by operation. If the mesial condyle, rather than the lateral, has been displaced, the bayonet incision must be placed on the inner aspect of the knee, in which case care should be exercised to preserve the internal saphenous nerve.

Whether plaster immobilization or suspension in a hinged splint should be used after operation is optional. We believe that if the fracture or fractures have been well stabilized by the bolt, suspension is sufficient. Early exercises can be carried out in the splint and at the end of a 6 weeks' period, the patient is allowed up on crutches, and with little weight-bearing in a light hinged brace to prevent any tendency to valgus deformity of the knee.

If the fracture is a simple, not comminuted one, it is possible that manipulation and compression, followed by plaster, will be sufficient. For the minor displacements or depressions or both, manipulation and plaster fixation may improve the situation. As in all fractures of weight-bearing joints, delayed weight-bearing must be practiced. Crutches must be used for a period of 2 to 6 months, depending upon the severity of the injury. Any tendency to valgus position of the knee must be prevented by the use of a hinged brace and Thomas heel.

ANALYSIS OF CASES FROM THE MASSACHUSETTS GENERAL HOSPITAL

From 1930 to 1945 inclusive, we treated in our clinic a total of 69 fractures of the tibial condyles involving the knee joint. An earlier series of 29 cases from 1923 to 1930 was reported by Barr (10) in the Massachusetts General Hospital Fracture Book, making a total of 98 cases.

In the 1923 to 1930 series, of 22 end-result cases, 17 were treated by nonoperative means and only 5 by surgery, one operation being an arthrodesis for painful traumatic arthritis, and 2 were compound fractures and simply débrided, thus leaving only 2 simple fractures treated by open reduction and internal fixation. In the more recent series, 1930 to 1945, 40 patients were treated by nonoperative means and 29 were subjected to surgery. Many of the 40 patients in the nonoperative group presented minor fractures with a clinical pic-

TABLE I.—TYPES OF INJURY SUSTAINED IN 29 MAJOR FRACTURES INVOLVING THE TIBIAL CONDYLES

	Cases
Lateral tibial condyle and head of fibula	7
Lateral tibial condyle	14
Medial tibial condyle	1
Medial tibial condyle and head of fibula	1
Lateral tibial condyle, compound and comminuted	2
Lateral tibial condyle, old	4
1. Removal of bolt	
1. Excision bone cyst	
1. Excision lateral meniscus	
1. Excision bone spicule	
Total	29

ture of ligamentous strain only and did not require prolonged treatment. Of the 29 operative cases in the latter series, 16 were male and 13 female, with an average age of 47 years. Table I shows types of injury in the 29 cases.

Of the 29 cases, 22 were simple fresh fractures suitable for open reduction and internal fixation. We add to these 2 similar cases from the 1923 to 1930 series, making a total of 24 (Table II).

In comparing the two series of cases, it is obvious that there has been an increasing tendency in our clinic to treat displaced fractures of the tibial condyles by surgical means. This has happened for 2 reasons: (1) we believe that most of these fractures cannot be reduced by manipulation, and (2) the improvement in operative technique by members of the Fracture Clinic during the past 10 or 15 years.

We are still not satisfied with some of our anatomical repositions. These partial failures have been due to the inexperience of some of the operators and to the severe comminution of some of the fractures. In the 1923 to 1930 series, of 2 operative cases, both patients obtained excellent results and were rated A-4, E-4, F-4. In the 22 patients operated upon in 1930 to 1945, 21 were restored to their former economic status and 18 had acceptable results, from an anatomical and functional standpoint.

TABLE II.—OPERATIVE PROCEDURES USED IN 24 CASES OF OPEN REDUCTION AND INTERNAL FIXATION OF TIBIAL CONDYLE FRACTURES

Excision of semilunar cartilage; reduction of fracture; bolt fixation	15
Excision of lateral semilunar cartilage, reduction of fracture; introduction of tibial bone graft, bolt fixation	5
Reduction of fracture; screw fixation	4
Total	24

TABLE III.—END RESULTS IN 24 FRACTURES TREATED BY OPEN REDUCTION AND INTERNAL FIXATION

A-4, E-4, F-4	8
A-4, E-4, F-3	2
A-3, E-4, F-3	6
A-3, E-4, F-4	4
A-3, E-3, F-3	1
A-3, E-1, F-3	1
A-2, E-3, F-2	1
A-2, E-4, F-2	1
	24

Rating 0 from 0% to 12½%; rating 1 from 12½% to 37½%; rating 2 from 37½% to 62½%; rating 3 from 62½% to 87½%; rating 4 from 87½% to 100%.

The use of the letters A, F, E, signifies: anatomic result, functional result, economic result.

CONCLUSIONS

1. Many fractures of the tibial condyles with more than a moderate degree of displacement should be treated by open reduction and internal fixation.

2. The surgeon undertaking such an operation must be well trained in meticulous joint surgery.

3. Preliminary manipulation and compression of many fractures of the lateral and medial tibial condyles may do harm to the joint surface of the tibia and make the subsequent open reduction more difficult.

4. Extensive comminuted fractures involving both tibial condyles may not be successfully reduced either by closed manipulation or open reduction.

These conclusions are based on a study of 98 cases, of which 24 patients were treated by open reduction and internal fixation.

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THE SURGICAL TREATMENT OF RECURRENT ACUTE PANCREATITIS BY ENDOCHOLEDOCHAL SPHINCTEROTOMY

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SURGICAL treatment of acute pancreatitis and especially of recurrent acute pancreatitis has been essentially palliative. Since 1901, when Opie focussed the attention of surgeons on the observation that acute pancreatitis could be produced by retrojection of bile into the pancreatic duct when the ampulla of Vater was occluded by a stone, the investigations of many surgeons and physiologists have been directed toward this problem. The operation of cholecystostomy or choledochostomy is but a temporary expedient to reduce the possibility of further passage of bile into an organ in which the disease process had already reached its apogee. The removal of stones from the gall bladder and bile ducts in recurrent pancreatitis and the prolonged drainage of the biliary tract are intended to be preventative measures and are so when obstruction at the ampulla is due to stone. Cholecystectomy in the absence of stones was advocated by Judd (20) and others for three reasons: (1) the removal of a muscular organ would prevent the forceful propulsion of concentrated bile into the pancreatic duct, (2) the absence of concentrated gallbladder bile would diminish the severity of its necrotizing action, since the severity of the process was shown by Flexner to depend partly on the bile salt concentration, and (3) cholecystectomy often resulted in relative atonicity of the sphincter of Oddi, as noted by others (9, 21). That this concept of Judd was justified was confirmed experimentally by Wangensteen on cats. Under his experimental conditions, the incidence of acute pancreatitis was reduced 50 per cent by cholecystectomy.

However, in all these operative procedures since the essential anatomy, a common passageway between the choledochus and the pancreatic duct, remains unchanged, it is obvious that the possibility of further obstruction due to factors other than stone might be anticipated. The recurrence of pancreatitis in patients after these operations confirms this fact.

The probability that attacks of acute pancreatitis might recur following the successful treatment of concomitant biliary tract disease was emphasized by the finding, that, in about 50 per cent of all cases of acute pancreatitis, the biliary tract was found to be normal. A solution of this puzzle was furnished by Archibald, who suggested in 1913 (1) that spasm of the sphincter of Oddi might produce sufficient temporary obstruction to enable bile to enter the pancreatic duct. He proved his case in 1919 (2), producing acute pancreatitis in cats by injecting bile into the biliary tract while temporary spasm of the sphincter was being induced by mechanical and chemical measures. Recent cholangiographic and kymographic studies on patients have confirmed his opinion that the human sphincter of Oddi was a highly labile muscle. Spasm of this muscle was occasionally found postoperatively (14, 16). Such drugs as morphine, local application of irritants such as hydrochloric acid, and even the response to emotional stimuli could produce spasm of the sphincter in the human (Figs. 1, 2, 3). Further, as a result of this spasm either found incidently or produced by pain or drugs, lipiodol or other radio-opaque substances could be seen in cholangiographic studies to enter the pancreatic duct (Figs. 4, 5, 6, 7) when it joined the bile duct above the sphincter of Oddi.

Obviously, if obstruction at the ampulla of Vater by spasm converts the bile and pancreatic ducts into a common channel leading to

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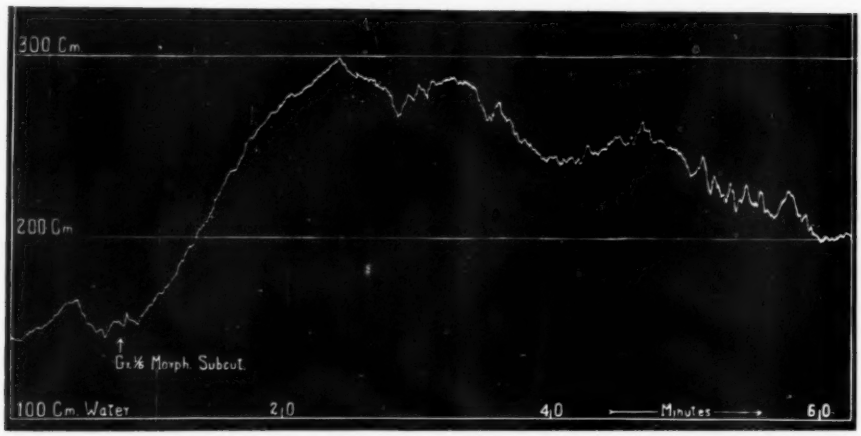

Fig. 1. Effect of morphine on the sphincter of Oddi. Kymographic tracing of the resistance of the human sphincter of Oddi shows that following the administration of ⅙ grain of morphine the normal resistance of the sphincter (150 millimeters of water) rises to 300 millimeters and gradually subsides to 200 millimeters in 1 hour.

the production of acute pancreatitis, the answer should be to cut the sphincter of Oddi or otherwise to destroy its function. However, a number of factors have so far prevented the general acceptance of this procedure. Among these considerations may be mentioned the danger of opening the duodenum to cut the sphincter, the difficulty of cutting the sphincter with certainty transduodenally, and the fear that cholangitis might be produced by duodenal reflux as a result of its destruction. However, the greatest deterrent to the adoption of this operation was the lack of complete conviction among surgeons themselves to the effect that acute pancreatitis was attributable entirely to biliary reflux.

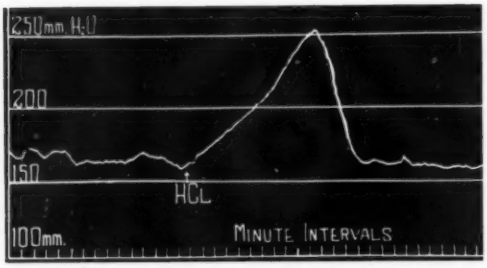

Fig. 2. Effect of 10th normal hydrochloric acid (local application) on the sphincter of Oddi. Intraduodenal installation of hydrochloric acid causes immediate spasm of the human sphincter of Oddi, the resistance to flow rising from 150 to 250 millimeters of water. The effect lasts for about 10 minutes or until the acid is washed away with water.

Aside from a few cases due to trauma, hematogenous infection, or interference with the blood supply to the organ by infarction or embolus, it was felt that acute pancreatitis might be produced by factors other than biliary reflux. Spread of infection from the gall bladder through the lymphatics (12) and intrapancreatic obstruction due to hyperplasia of the pancreatic duct epithelium (26) were also considered as etiological factors. Finally authentic cases were described in which acute pancreatitis was found in the absence of a possible common passageway between the biliary and pancreatic ducts, since these opened separately into the duodenum (11, 19). However, the consensus seemed to indicate that at least 60 per cent of all cases of pancreatitis were due to reflux of bile into the pancreas. Certainly most operative procedures were based on this assumption.

In recent years the conservative treatment of acute pancreatitis has gained almost general advocacy (17, 23, 24). In the great majority of cases, this was made possible only by the development of the serum amylase test, by means of which the diagnosis could be made without exploratory laparotomy. The con-

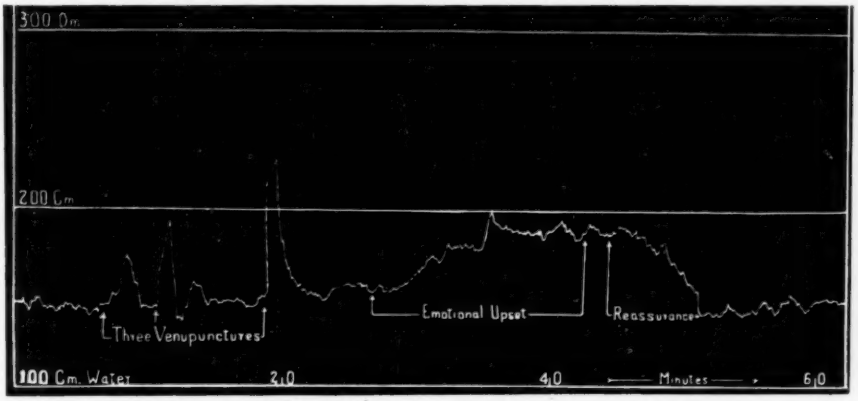

Fig. 3. Effect of pain and emotion on the tonus of the sphincter of Oddi. The insertion of a needle into the antecubital vein caused a marked rise in the tonus of the sphincter as a result of fear and pain. When the patient was reminded of the neglect of her only daughter, she began to cry, and the tonus of the sphincter increased as the result of a feeling of hostility and resentment. When she was assured that her daughter had telephoned and would come to see her, the sphincter could be seen to relax.

servative treatment led to a marked lowering of the mortality rate for acute pancreatitis. However, many of the patients who were thus treated and saved an operation returned for treatment because of recurrent attacks of acute pancreatitis, each attack carrying with it the possibility of either severe complications or a lethal outcome.

Two groups could be distinguished: (1) those with a normal biliary tract, described in a classic paper by Comfort and his associates, and (2) those who had previous operations, removal of gall stones, cholecystostomy or choledochostomy with drainage of the biliary tract for prolonged periods, cholecystectomy or cholecystogastrostomy. It is these patients, several of whom will be described, who force us to consider the need for developing a definitive surgical procedure for their treatment.

CASE REPORTS

CASE 1. H. W., No. 58318-46, a 36 year old colored male, with a 1 year history of recurrent attacks of severe epigastric pain accompanied by nausea and vomiting, was admitted to the Third (N.Y.U.) Surgical Division of Bellevue Hospital on December 2, 1946. Various diagnoses such as gastritis or duodenal ulcer had been made by different physicians. For the past 2 months he had been on a peptic ulcer regimen and had stopped drinking, a habit to which he had been excessively addicted. However, on November 28, 1946, he had indulged in a large Thanksgiving dinner, including a number of alcoholic drinks, and subsequently developed moderate epigastric pain which lasted until December 2, 1946. On this day he suffered a sudden onset of severe prostrating epigastric pain which radiated to the left shoulder and left groin. On admission to the hospital 8 hours later, he was found to have generalized superficial abdominal tenderness, with marked tenderness in the epigastrium on deep palpation. Temperature was 100 degrees, white blood count 13,400. A flat plate of the abdomen failed to reveal any free air in the subphrenic regions. The serum amylase, carried out the day after admission, was 260 milligrams per cent, and a diagnosis of acute pancreatitis was made. The amylase fell to 180 milligrams per cent the following day and to 161 milligrams per cent on the 4th day of the attack. By then his symptoms had disappeared and he was prepared for cholecystographic studies. That night he had a recurrence of pain and the following morning his serum amylase had risen to 302 milligrams per cent. Nevertheless, he was given a routine fat meal after a preliminary x-ray examination and 2 hours later his serum amylase had risen to 387 milligrams per cent (Fig. 8). The cholecystogram revealed a normally functioning gall bladder. X-ray examination of his stomach and duodenum failed to reveal any abnormality. He signed out against advice on December 17, 1946 before further studies could be done.

CASE 2. O. T., No. 12709-47, a 44 year old white man, was admitted to Bellevue Hospital on March 10, 1946, with complaints of severe epigastric and right upper quadrant pain, abdominal distention, and vomiting. He gave a 12 year history of chronic alcoholism, and an 18 month history of recurrent attacks of epigastric pain associated with bouts of acute alcoholism. He had been treated at a number

Fig. 4.

Fig. 5.

Figs. 4 and 5. Visualization of the pancreatic duct as a result of increased tonus of the sphincter of Oddi. Incidental spasm (Fig. 4) results in passage of injected iodized oil into the main pancreatic duct (one arrow) and thence into the accessory pancreatic duct of Santorini (two arrows). Pain produced by sudden distention of the common bile duct results in reflex spasm of the sphincter of Oddi and allows injected diodrast (33%) to pass up the pancreatic duct, completely outlining it to the tail (arrow).

Fig. 6.

Fig. 7.

Figs. 6 and 7. Visualization of the pancreatic duct as a result of spasm of the sphincter of Oddi produced by morphine. Following the administration of 1/6 grain of morphine 1 hour previously, the sphincter of Oddi became sufficiently spastic to enable the iodized oil to fill the whole pancreatic duct (arrow) in a patient whose gall bladder had been removed 2 weeks previously, and the cystic duct drained. On slight rotation of the patient (Fig. 7) the junction of the ducts was clearly visualized.

of different hospitals where various diagnoses such as gastritis, cirrhosis of the liver, duodenal ulcer, and delirium tremens were made. This last attack began suddenly 33 hours before admission following a meal eaten after a bout of alcoholism and starvation lasting for 5 days. On admission he appeared acutely ill. His temperature was 98 degrees, white blood count 16,400. There was considerable abdominal disten-

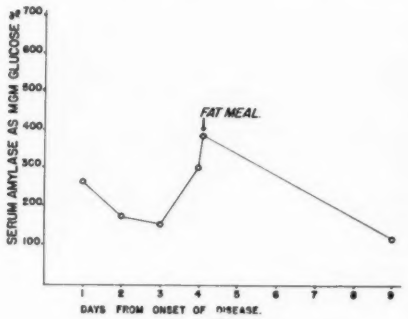

Fig. 8.

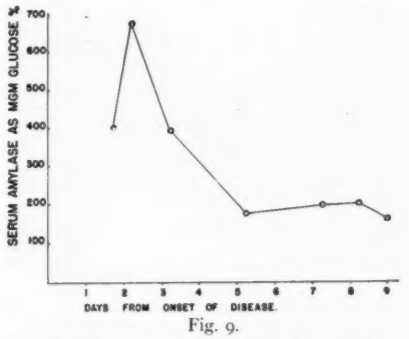

Fig. 9.

Figs. 8 and 9. The serum amylase test as an index of the progress of acute pancreatitis. In Case 1 (Fig. 8), the serum amylase dropped to 161 milligrams per cent on the 4th day, but following a fat meal there was a recurrence of symptoms and the serum amylase confirmed the recurrence of acute pancreatitis. In Case 2 (Fig. 9), the serum amylase indicated the gradual recovery from the disease.

tion and marked tenderness on deep palpation in the epigastrium and right upper quadrant. X-ray examination of the abdomen failed to reveal free air under the diaphragm. A serum amylase of 400 milligrams per cent established the diagnosis of acute pancreatitis. Under Miller-Abbott tube suction and intravenous hydration and nutrition he improved rapidly, and his serum amylase, although it rose on the 2nd day of admission, gradually subsided (Fig. 9). He developed delirium tremens on the 3rd hospital day and was transferred to the psychiatric division. He improved under appropriate treatment. A cholecystogram showed an apparently normal gall bladder, with rather poor concentrating power. X-ray films of the stomach and duodenum failed to reveal any abnormality. He signed out against advice on April 1, 1947.

These 2 patients might conceivably do well on a regimen of frequent small meals and total abstinence from alcohol. However, the danger of recurrent attacks, one of which might be lethal, would always be present. An operative procedure which would prevent biliary reflux, if such an anatomical condition were present, should be considered.

The following case illustrates many of the serious complications of recurrent acute pancreatitis, one of which nearly led to death.

CASE 3. F. J., No. 51642-46, a 34 year old white male, was admitted to Bellevue Hospital for the first time on October 30, 1946, with a 10 year history of recurrent attacks of severe epigastric and left upper quadrant pain, associated with chills and fever. The attacks would last from 1 to 4 days, occur frequently at irregular intervals, although there were periods of 1 to 2 years when he was completely asymptomatic. On 2 occasions the attacks were so severe that he was hospitalized. During a prolonged severe attack in 1944, the abdomen was explored and an acutely inflamed pancreas, with the stomach, duodenum, and transverse colon adherent to it, was found. Cholecystostomy was performed and biliary drainage was carried out for 6 weeks. Up to the time of this last admission, he had never felt quite well, suffering from a dull aching epigastric pain and recurrent attacks of acute pain, chills, and fever for which he received antimalarial treatment on several occasions in army hospitals. While under observation at Bellevue Hospital, he developed a bilateral subphrenic abscess apparently due to rupture of an infected pancreatic cyst. These subphrenic abscesses were drained. Following recovery after an extremely stormy course, the following observations were noted: (1) calcification of the head and tail of the pancreas (Fig. 10); (2) a large and swollen pancreas as evidenced by an increase in the duodenal curve (Fig. 11) and by anterior displacement of the stomach (Fig. 12); (3) secretin test on two occasions revealed that the secretion of pancreatic juice was diminished over one-half and that the concentration of amylase was one-third of normal; (4) a diabetic type of glucose-tolerance curve 5 months after his last severe attack (Fig. 13). Since his discharge he has had several moderate attacks of pain, has felt weak, and has failed to gain weight.

This patient demonstrates all the serious complications of acute recurrent pancreatitis. The prognosis is extremely poor. At best it will mean recurrent attacks of pain, increasing inability to digest his food, and an increasing tendency to develop a more severe grade of diabetes. However, he may develop a recurrence of a pancreatic cyst, or even a fatal pancreatitis. It would seem that if a reflux mechanism could be proved in this case, destruction

Fig. 10.

Fig. 11.

Fig. 12.

Figs. 10, 11, and 12. Result of recurrent attacks of severe acute pancreatitis over a period of 10 years (Case 3). Calcification of the head and tail of the pancreas (Fig. 10) is clearly shown (arrow). The enlargement of the pancreas is evidenced by increase in the curve of the duodenum (Fig. 11) and by anterior displacement of stomach (Fig. 12).

of his sphincter of Oddi should be considered. However, his condition has progressed so far that a total pancreatectomy may have to be done to cure him.

The next patient illustrates recurrent acute pancreatitis due to obstruction of the papilla of Vater by a stone.

CASE 4. D. C., No. 43136-47, a 37 year old colored woman, was admitted for the first time to the 3rd Surgical Division of Bellevue Hospital on September 11, 1946, with a 3 year history of attacks of severe epigastric pain radiating to the back. One month previously she was treated at another hospital for peptic ulcer. The day before admission she developed a severe attack for which she was admitted to another hospital, and then transferred to Bellevue Hospital.

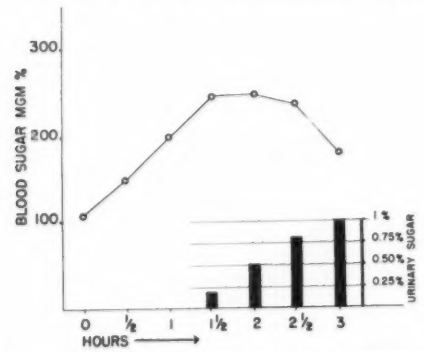

Fig. 13. The progressive destruction of the pancreas by recurrent attacks of pancreatitis in Case 3 involves not only the acinar cells but the islet cells as well, as shown by the diabetic type of glucose tolerance curve.

On admission she appeared to be quite ill. Temperature, pulse, and white blood cell count were markedly elevated. The abdomen was distended, and tenderness was marked in the epigastrium and right upper quadrant. X-ray films of the abdomen revealed distended small bowel, but no fluid levels or free air. A serum amylase taken soon after admission was 256 milligrams per cent. A diagnosis of acute pancreatitis was made, and the patient treated by Miller-Abbott tube suction and intravenous hydration. The symptoms subsided rapidly and the serum amylase fell to normal on the fourth day of her illness (Fig. 14). A cholecystogram, done on the ninth day of her illness, failed to visualize the gall bladder. The routine fat meal given with this procedure induced another attack of epigastric pain. Blood amylase taken the next day was 500 milligrams per cent. This high amylase subsided rapidly to normal figures. X-ray examination of the stomach and duodenum was reported normal. A diagnosis of chronic cholecystitis in addition to recurrent acute pancreatitis was made, and an exploratory operation was carried out on October 3, 1946. A thin walled gall bladder full of small stones was found. The cystic duct was dilated and contained 2 stones. The common duct was 2 centimeters in diameter, inflamed, and thickened. A number of small stones could be palpated inside it. The head of the pancreas was found somewhat indurated.

After ligating the cystic duct, a needle was introduced into the common duct and lipiodol was injected. A cholangiogram (Fig. 15) revealed the presence of the stones, but the pancreatic duct was not visualized. The gall bladder was removed, and

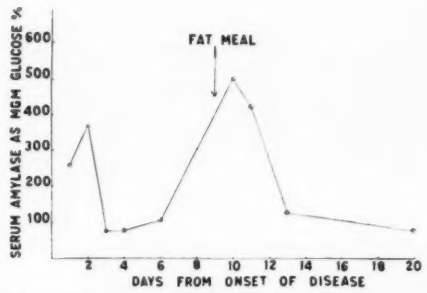

Fig. 14. Serum amylase determinations in Case 4 demonstrate the recovery from an attack of acute pancreatitis and the recurrence of the disease following the administration of a fat meal.

Fig. 15. Cholangiogram performed on the operating table in a case of acute pancreatitis due to intermittent obstruction of the papilla of Vater by a small stone. The common duct is seen to contain stones, but the pancreatic duct is not visualized due to absence of sufficient obstruction at this time.

the common duct was opened. After removing the calculi, a catheter was inserted into the distal part of the duct for a distance of 2 centimeters and secretin administered intravenously. About 4 cubic centimeters of rather mucoid colorless fluid was obtained from the catheter. This proved to be pancreatic juice, since on analysis later on it was found to contain 1,000 milligrams per cent of amylase. The common bile duct was drained by a T-tube.

Two weeks later, cholangiographic studies revealed a spastic sphincter (Fig. 16). Following the administration of morphine, a long narrow rather fixed intramural portion of the bile duct could be visualized (Fig. 17). This did not change after the administration of amyl nitrate. Several cholangiographic studies showed the same picture. The pancreatic duct could not be visualized by the use of morphine. However, closure of the T-tube produced no symptoms. The tube was removed 40 days after operation. The fistula closed immediately, and she has been symptom-free since.

We consider this patient one who has a common biliary-pancreatic passageway (reflux mechanism) as proved by the presence of pancreatic juice in the common bile duct after the administration of secretin. The sphincter of Oddi was not sectioned since it was felt at the time of operation that the reflux of bile into the pancreas was due to obstruction by stone and not by spasm. However, since the anatomical

Fig. 16.

Fig. 17.

Figs. 16 and 17. Acute pancreatitis due to obstruction of the papilla of Vater by a stone (Case 4). Two weeks after removal of the common duct stones, cholangiographic studies show that the sphincter has a normal tonus (Fig. 16). Following the administration of morphine the whole biliary tract is outlined, but the pancreatic duct is not visualized. The intramural portion of the common duct is narrowed by compression of the duodenal wall musculature (arrow).

Fig. 18. Visualization of the pancreatic duct at operation in a case of recurrent acute pancreatitis of 20 years' duration (Case 5). As a result of spasm of the sphincter of Oddi produced by hydrochloric acid injected through a duodenal tube, the iodized oil passed up the pancreatic duct (arrow).

condition (a common passageway) remained intact, the prognosis has to be guarded since recurrence remains a possibility.

The next patient presented represents the type of case in which two previous operations on the biliary tract had failed to prevent recurrences of extremely severe attacks of pain.

CASE 5. M. H., No. 10199-47, was a 51 year old woman with a history of a cholecystectomy 20 years previously for attacks of severe epigastric pain. The recurrent attacks persisted and 7 years ago, following an attack of severe epigastric pain accompanied by

Fig. 19. The piece of tissue removed by the endocholedochal sphincterotome from the sphincter of Oddi in Case 5 shows connective and muscle tissue, glands of the common bile duct wall, and duodenal mucosa.

jaundice (icteric index 40), an exploratory operation was carried out by an extremely able surgeon. The common bile duct was moderately dilated but contained no stones. A chronic pancreatitis, as evidenced by a hard irregular mass in the head of the pancreas, was found. To make certain that no obstruction existed, a probe was passed down the choledochus into the duodenum which was opened to confirm the passage of the probe. Common duct drainage was maintained for 2 weeks. Attacks recurred 1 year later and steadily grew worse both in severity and frequency, in the last 6 months occurring every 2 weeks. She was admitted to 3rd Surgical Division of Bellevue Hospital on February 24, 1947, 3 days after the onset of an attack of severe epigastric and left upper quadrant pain, associated with nausea, vomiting, and fever. Her temperature was 102.4 degrees, pulse 110, white blood count 10,900. The abdomen was distended. X-ray examination revealed no free air beneath the diaphragm but showed distended small bowel with fluid

Fig. 20.

Fig. 21.

Figs. 20 and 21. Cholangiographic studies in Case 5, two weeks after sphincterotomy, show the free entrance of iodized oil into the duodenum (Fig. 20). Following application of acid to the duodenum (Fig. 21), the pancreatic duct is not visualized. Under similar conditions prior to sphincterotomy the pancreatic duct was visualized (Fig. 18).

levels. Miller-Abbott tube suction and intravenous hydration were instituted. The next day the temperature rose to 105.4 degrees but subsided rapidly under treatment. The serum amylase on the fourth, fifth, and sixth days of the attack was 22, 40, and 60 milligrams per cent, respectively. Following a fat meal on the sixth day it rose to 72 milligrams per cent. On March 4, 1947, the symptoms recurred for 1 day with a rise of temperature to 102 degrees. The serum amylase was 84 milligrams per cent and the blood sugar 201 milligrams per cent. A secretin test on March 20, 1947 revealed a normal response of pancreatic secretion in regard to volume but a very high concentration of amylase. The serum amylase rose from 84 milligrams per cent at the beginning of the test to 160 milligrams per cent at the end of the test. A glucose tolerance curve was normal. X-ray examination of the stomach and duodenum was reported to be normal. On the basis of the past history and findings, and by a process of exclusion, it was felt that this patient was suffering from attacks of recurrent acute pancreatitis in spite of the fact that a high serum amylase was not detected during the period of observation. The extremely low amylase figures found after the first attack also suggested the recovery phase of pancreatitis as noted by McCorkle and Goldman.

It was felt that the severity of the patient's symptoms justified section of the sphincter of Oddi, if it could be shown that a common passageway existed between the bile and pancreatic ducts. Operation was performed on March 24, 1947. The pancreas was found uniformly enlarged and indurated. The common bile duct was exposed and found moderately dilated. The remnant of the cystic duct, about 2 centimeters long, left behind at the cholecystectomy performed 20 years previously, was opened and

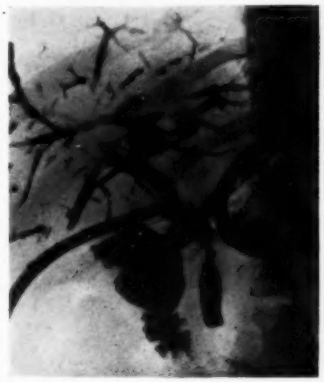

Fig. 22. The administration of morphine in Case 5 two weeks after sphincterotomy shows compression of the intramural portion of the common bile duct due to increased tonus of the duodenal wall. This acts as a one-way valve and prevents duodenal reflux after the sphincter of Oddi is cut.

a catheter tied into it. Lipiodol was injected slowly into the biliary tract; simultaneously 5 cubic centimeters of 10th normal hydrochloric acid was injected into the duodenum by means of a duodenal tube passed preoperatively. This was done to produce spasm of the sphincter of Oddi without producing contraction of the duodenal musculature, in order to set up the optimum conditions for visualization of the pancreatic duct (15). A cholangiogram obtained under these conditions clearly showed the pancreatic duct and proved the presence of reflux (Fig. 18). Accordingly the sphincterotome to be described later was passed into the duodenum

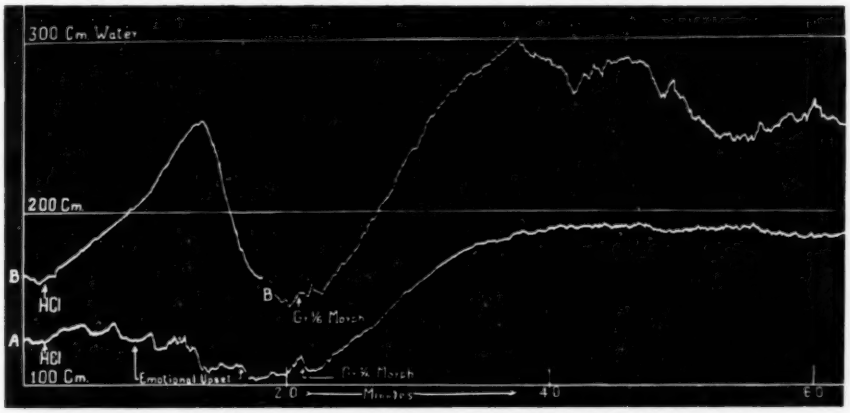

Fig. 23. Kymographic tracing *A* of the resistance to flow of bile into the duodenum in Case 5 indicates that the sphincter of Oddi is destroyed functionally since there is no response either to local application of acid or to emotional stimuli. The response to morphine is limited to its action on the duodenal musculature. This tracing can be compared to the response of the intact sphincter to acid and morphine (*B*, superimposed).

Fig. 24.

Fig. 25.

Figs. 24 and 25. Injection of iodized oil shows considerable spasm of the sphincter of Oddi (Fig. 24) since the hepatic ducts are outlined to a considerable extent before the oil passes into the duodenum. At the same time, a portion of the pancreatic duct (arrow) is filled. The junction of the common and pancreatic ducts at the ampulla of Vater is clearly visualized. Following the administration of morphine (Fig. 25) the whole biliary tract is outlined. The increased tonicity of the duodenal wall as a result of morphine action causes compression of the intramural portion of both the common and pancreatic ducts, illustrating perfectly how the duodenal wall acts as a one-way valve. The ampullary junction of these ducts is, however, still clearly outlined (arrow).

through the common duct and the sphincter sectioned. The piece of tissue removed from beneath the blade showed the presence of duodenal mucosa, common duct mucosa, and muscle tissue (Fig. 19). A T-tube was placed into the common bile duct and the abdomen closed. Two weeks after operation a duodenal tube was passed and cholangiographic studies were performed again; lipiodol could be seen to enter the duodenum easily (Fig. 20). When hydrochloric acid was injected into the duodenum by means of a duodenal tube, spasm of the muscularis mucosa of the duodenum occurred, but the pancreatic duct could not be visualized (Fig. 21). These findings clearly show that under the same conditions that prevailed at operation, reflux of lipiodol into the pancreas did not occur. Close observation of the cholangiogram also showed that the intramural part of the common bile duct was intact. Spasm of the duodenal wall produced by the injection of morphine completely closed off this intramural portion of the duct (Fig. 22). Thus, destruction of the sphincter of Oddi, to prevent reflux of bile into the pancreatic duct, had been achieved without interfering with the mechanism which prevented duodenal reflux. It was evident that every time this patient's duodenum contracted the intramural part of the bile duct was compressed and acted as a one-way valve.

Kymographic studies of the resistance to the flow of bile into the duodenum confirmed the cholangiographic observations (Fig. 23). The application of acid to the duodenal mucosa did not increase the resistance to the flow of bile. An emotional tearful upset induced by discussing her past suffering had no effect on the sphincteric resistance. The injection of morphine had only a moderately spastic effect. The effective reduction, due to sphincterotomy, on the spasm produced either locally (acid) or generally (morphine) could be visualized most graphically by superimposing tracings produced by these drugs on patients with an intact sphincter of Oddi. Following these observations on the patient, the T-tube was removed and the fistula ceased to discharge bile on the same day.

The evidence indicates that in this last patient reflux of bile into the pancreas should not occur again. Whether a cure will result depends on the etiology of her recurrent pancreatitis. If this operation does not cure her, it would seem that other procedures will have to be devised for this condition. Experience, as a result of the Whipple operation for carcinoma of the head of the pancreas, may lead to the development of such procedures as subtotal or total pancreatectomy for recurrent acute pancreatitis. Due to its extraordinary regenerative powers (13), only a small portion of the

pancreas implanted into the jejunum should prevent both diabetes and steatorrhea.

Archibald first suggested sphincterotomy for pancreatitis in 1913 (1), and first performed it transduodenally in 1918 on a patient suffering from recurrent attacks of acute pancreatitis. In all, he operated on 8 patients. He was able to follow 6 of these patients and found them symptom-free, without evidence of cholangitis (3). The objections to performing this operation transduodenally were due to the danger of opening of the duodenum, the difficulty of finding the papilla of Vater without opening the bile duct and passing a probe down into the duodenum, and, most important of all, the difficulty of cutting of the sphincter transduodenally without destroying the musculature of the duodenum through which the common bile ducts courses obliquely. It is this oblique course through the duodenal wall, as Coffey had shown in devising his operation for ureterocolic anastomosis, which prevents duodenal reflux. Every time the duodenum contracts, both the bile and pancreatic ducts are closed off by the valve-like action of the duodenal musculature (Figs. 24 and 25). At Archibald's suggestion, an effort was made to develop an instrument which would section the sphincter of Oddi safely through an opening in the common bile duct and not through the duodenum, and at the same time would not cut the duodenal musculature. Such an instrument was finally perfected by Colp and Doubilet (9) (Figs. 26, 27, 28), and was used successfully in the treatment of dyskinesia of the sphincter of Oddi (4, 5, 7, 8). This instrument was also used by Colp (6) in 1945 in an

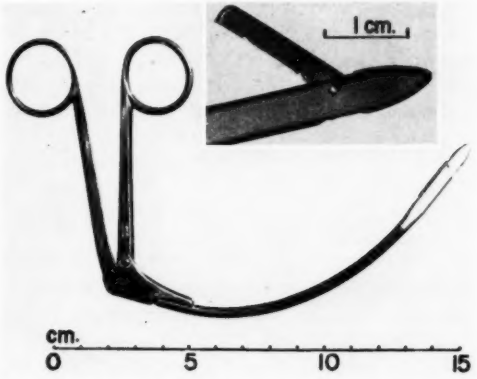

Fig. 26. Endocholedochal sphincterotome. The length and curvature of the instrument are adapted to insertion into the duodenum through the common duct. Since the handle and knife are in the same side and plane only the anterior free lip of the papilla of Vater can be cut. The length of the effective section is 1 centimeter.

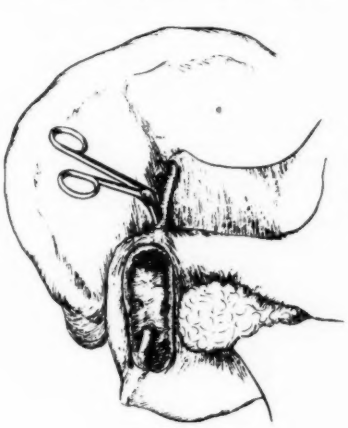

Fig. 27.

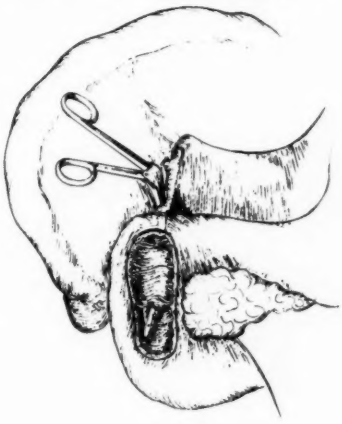

Fig. 28.

Figs. 27 and 28. Endocholedochal sphincterotomy. The instrument is inserted through the common duct into the duodenum until it elevates the anterior duodenal wall (Fig. 27). The blade is then opened to convert the instrument into a hook and the instrument withdrawn until it catches the papilla. On closure, the sphincter of Oddi is sectioned in one plane.

attempt to prevent reflux in a patient who developed an acute perforation of the common bile duct as a result of retrojection of the pancreatic juice into the bile duct. Subsequent x-ray and kymographic studies failed to show evidence of division of the sphincter.

The curve of the instrument with relation to the anatomy of the bile duct, duodenum, and the papilla of Vater is constructed so that it can be used without danger. It will destroy the function of the sphincter of Oddi without interfering with the intramural portion of the common bile duct and so accomplishes the purpose of the operation without danger of a resultant cholangitis.

The cholangiographic and kymographic studies presented here not only corroborate each other but also indicate that the resistance to flow of bile into the duodenum is made up of two components: (1) the sphincter of Oddi and (2) the duodenal musculature. The resistance of the sphincter of Oddi under normal conditions is probably a constant factor. This resistance may be modified by the presence of acid in the duodenum or by the emotional reactions of the individual. On the other hand, the resistance produced by the duodenum is equivalent to about 100 to 120 millimeters of water and is increased only during a phase of the passage of a peristaltic wave, or by a general increase in intestinal tonus.

Fundamentally, the function of the sphincter of Oddi is to increase the resistance to the flow of bile into the duodenum to an extent just sufficient to fill the gall bladder. In animals, destruction of the sphincter leads to complete loss of function of the gall bladder (9). It ceases to fill and therefore to empty, and becomes a collapsed flaccid diverticulum. On physiological principles, the indications are clear that when the sphincter of Oddi is destroyed the gall bladder should be removed. This point should be considered in any future work on the sphincter of Oddi.

The first 2 cases presented are typical of recurrent acute pancreatitis in patients in whom the biliary tract is normal. They pose the problem as to the treatment which would be required to prevent recurrences. The third case represents the serious complications, short of death, that may ensue as a result of neglecting to treat these patients with recurrent acute pancreatitis. The fourth case represents the type in which the biliary tract is involved. Merely removing the gall bladder and the common duct stones is not the optimum treatment, since the basic anatomical condition, a common passageway between biliary and pancreatic ducts, has not been changed. Case 5 shows definitive treatment of recurrent acute pancreatitis if disease is due to biliary reflux.

CONCLUSIONS

1. Reflux of bile into the pancreatic duct should be prevented by cutting the sphincter of Oddi.

2. Endocholedochal sphincterotomy can be performed with safety without danger of producing cholangitis by duodenal reflux.

3. Endocholedochal sphincterotomy should be the definitive surgical procedure in the treatment of recurrent acute pancreatitis if reflux of bile into the pancreas through a common biliary pancreatic passageway can be demonstrated.

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HYPOSPADIAS WITH ENLARGEMENT OF THE PROSTATIC UTRICLE

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THE prostatic utricle is of interest because it may serve as an indicator of intersexuality in the male. A number of instances of cystic dilatation of the utricle and of greater degrees of persistence of the muellerian ducts are recorded in the literature.[1] The association of enlargement of the utricle with other genital defects such as hypospadias and incomplete testicular descent has long been known (1, 42). It has been suggested that hypospadias in the male is an intersexual manifestation rather than an isolated fusion defect (13, 15). If this theory is correct, congenital enlargement of the utricle might be expected to occur frequently in hypospadic individuals; and the degree of differentiation of the muellerian ducts in the female direction should vary in proportion to the severity of the penile deformity. This paper is based upon a study of 14 unselected males undergoing surgical treatment for hypospadias at the University of California Hospital. In 10 of these, an abnormal degree of development of the uterovaginal tract has been found. There is also a close correlation between the degree of differentiation of the structures of muellerian derivation and the severity of the penile and other genital anomalies (Table I).

MATERIAL AND METHODS

The cases were selected as follows: (1) they were hospitalized for surgical treatment of congenital hypospadias; (2) testes were demonstrated either by palpation or by laparotomy and biopsy; and (3) permission for cystoscopy was obtainable. The ages of the subjects varied from 1 to 29 years. Minor degrees of hypospadias are not represented since they are not treated surgically. Testicular biopsy was performed only twice. In the others, the gonadal sex was based upon the physical examination.

The urethra was examined endoscopically and the utricle explored with a catheter. When the catheter could be passed for a distance of 2 centimeters or more, x-ray films were taken before and after injection of a radio-opaque substance. Twice it was possible to pass the endoscope directly into a vagina. There were no untoward reactions. Table II shows the normal length of the utricle according to various authors. For the purposes of this study the dividing line between normal and abnormal size of the utricle was chosen as the base of the prostate for the child and at a distance of 2 centimeters from the utricular orifice for the adolescent and adult. In only one instance (Case 4) was a measurement close to the dividing line obtained.

ABSTRACTS OF CASES

CASE 1. C.F. This boy was examined July 13, 1945, at the age of 11 years. There were no siblings. The penis was of normal size with a false meatus in the glans. The urethral meatus was 2 millimeters proximal to the coronal sulcus, and moderate chordee was present. The scrotum, scrotal contents, and prostate were normal. Cystourethroscopy gave normal findings. The utricle admitted a catheter for 5 millimeters.

CASE 2. M.O. This man was examined August 28, 1944, at the age of 29 years. He had one normal brother. The penis was of normal size with the meatus midway between the penoscrotal juncture and the coronal sulcus. Moderate chordee was present. The scrotum, scrotal contents, and prostate were normal. Endoscopic examination of the bladder and posterior urethra gave normal findings. The utricle admitted a catheter for 5 millimeters. The ejaculatory ducts were easily identified.

CASE 3. H.D. This patient was examined December 12, 1943, at the age of 17 years. He had one normal brother and one normal sister. Hypospadias and imperforate anus were present at birth. Following proctoplasty at the age of 3 days, he developed a fistula between the bulbous urethra and the perianal scar. This fistula later was closed surgically. The penis was of normal size with the urethral meatus midway between the penoscrotal juncture and

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[1]Articles marked with asterisk in references at end of article.

TABLE I

Group	Case No.	Age in years	Testicles	Degree of hypospadias	Muellerian duct development	Other anomalies
I	1	11	Normal	Penile	Normal utricle	None
	2	29	Normal	Penile	Normal utricle	None
	3	17	Normal	Penile	Normal utricle	Imperforate anus
	4	23	Left, inguinal; right, normal	Penile	Normal utricle 2 cm. long	None
II	5	2	Normal	Penoscrotal	Enlarged utricle	Umbilical hernia
	6	2	Normal	Penoscrotal	Enlarged utricle	None
	7	14	Normal	Penoscrotal	Enlarged utricle	None
	8	21	Small; left fully descended, right in upper scrotum	Penoscrotal	Enlarged utricle	None
	9	8	Left, inguinal; right, normal	Penoscrotal	Enlarged utricle	None
	10	6	Both inguinal	Penoscrotal	Enlarged utricle	Premature birth
	11	1	Both inguinal	Perineal	Enlarged utricle	Premature birth
	12	22	Small; left fully descended; right, inguinal	Perineal	Enlarged utricle	Gynecomastia
III	13	3	Left absent; right, inguinal	Perineal	Uterus without tubes, vagina entering posterior urethra	Seminal vesicles absent; vasa incomplete
	14	20	Atrophic and pelvic	Perineal	Uterus with tubes, vagina entering anterior urethra	Prostate, seminal vesicles, and vasa absent

the coronal sulcus. Moderate chordee was present. The scrotum, scrotal contents, and prostate were normal. The bladder and posterior urethra were normal endoscopically. The utricle admitted a catheter for 1 centimeter. The ejaculatory ducts were identified.

CASE 4. W.R. This man was examined June 9, 1945, at the age of 23 years. He had one normal brother. The penis was at the lower limits of normal size. The meatus was midway between the penoscrotal juncture and the coronal sulcus, and moderate chordee was present. The right testicle was normal and fully descended; an atrophic left testicle was palpable outside the external inguinal ring. The prostate was normal. The bladder and posterior urethra were normal endoscopically. The utricle admitted a catheter for 2 centimeters but could not be distended by injection. The ejaculatory ducts were identified.

CASE 5. R.E. This child was examined January 7, 1944, at the age of 2 years. He had one normal sister. A congenital umbilical hernia was present. The penis was of normal size with the urethral meatus at the penoscrotal juncture and moderate chordee. The scrotum, scrotal contents, and prostate were normal. Cystourethroscopy showed a large utricular orifice in the normal position. Dimensions of the utricle as measured on the x-ray films were 2.0 by 0.6 by 0.6 centimeters.

TABLE II

Reference	Number of specimens studied	Length of normal utricle	Number of cases of enlargement of the utricle
McCarthy, et al. (1927)	20 adults	6 mm.	0
McMahon (1938)	23 adults	4–19 mm.	0
R. A. Moore (1937)	678 adults	4–16 mm.	7
Springer (1898)	62 infants	½–⅗ the distance from the verumontanum to the base of the prostate	1

CASE 6. G.C. (Fig. 1). This child was examined April 9, 1945, at the age of 2½ years. He had one normal sister. The penis was normal in size but with the meatus at the penoscrotal juncture and moderate chordee. The scrotum, scrotal contents, and prostate were normal. Urethroscopy showed a large utricular orifice surrounded by hymen-like flaps standing in a slight elevation representing the verumontanum. The right ejaculatory duct was identified. X-ray visualization showed a large utricle with several diverticula. The dimensions of the utricle were 4.5 by 2.0 by 1.0 centimeters.

CASE 7. G.A. This boy was examined September 13, 1945, at the age of 14 years. He had two normal brothers and one normal sister. The penis was normal in size but with the urethral meatus in the anterior portion of a partially cleft scrotum. Marked chordee was present. The testicles were normal and fully descended. The prostate was normal. Urethroscopy showed a mushroom-shaped verumontanum with a large utricular orifice. The ejaculatory ducts were not identified. The utricle measured 5.0 by 1.6 by 1.5 centimeters.

CASE 8. E.R. (Fig. 2). This young man was examined August 28, 1944, at the age of 21 years. There were no siblings. The penis was slightly smaller than normal. The meatus was in the anterior portion of a partially cleft scrotum. Marked chordee

was present. The testicles were slightly smaller and softer than normal. The left testicle was fully descended, but the right was in the upper scrotum. The prostate was normal. Urethroscopy showed replacement of the verumontanum by frond-like flaps of mucous membrane overlying the utricular orifice. The utricle measured 6.4 by 2.8 by 3.0 centimeters.

CASE 9. C.I. This boy was examined December 13, 1943, at the age of 8 years. There were no siblings. The penis was slightly smaller than normal with the meatus at the penoscrotal juncture and marked chordee. The scrotum was partially cleft. The right testicle was normal and fully descended. The left testicle lay just outside the external ring at this time but descended spontaneously 3 years later. The prostate was normal. The dimensions of the utricle were 3.3 by 1.6 by 1.4 centimeters.

CASE 10. D.U. This boy was examined May 11, 1945, at the age of 6 years. He was born after 7½ months' gestation. There were no siblings. The penis was slightly smaller than normal with the meatus at the penoscrotal juncture and marked chordee. The testicles were felt just outside the external inguinal rings, but could be brought easily into the partially cleft scrotum. The prostate was normal. The utricle measured 2.4 by 0.7 by 0.8 centimeters.

CASE 11. J.P. (Fig. 3). This patient was examined November 11, 1943, at the age of 14 months. There were no siblings. He was born weighing 1200 grams after 7 months' gestation. Growth and development were slow and the bone-age was retarded. The penis was small with the urethral meatus in midscrotum. Marked chordee was present. The scrotum was bifid. The right testicle was palpable at the external ring. The left testicle was not palpable at this time,

Fig. 1. Case 6. Dilated utricle with diverticula occurring in association with penoscrotal hypospadias.

but became palpable at the external ring at the age of 2½ years. A prostate was palpable, and the prostatic urethra was normal endoscopically. The utricle measured 2.5 by 1.0 by 0.9 centimeters.

CASE 12. W.S. This college student was examined September 5, 1944, at the age of 22 years. He had 3 normal brothers and 1 normal sister. His mother's brother was said to have a feminine appearance, but details were not available. The body con-

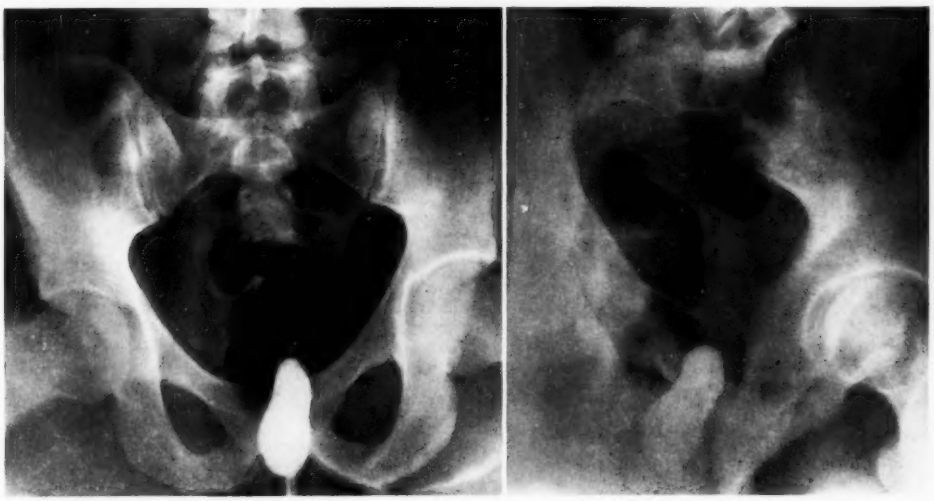

Fig. 2. Case 8. A large utricle filled by retrograde injection is shown in anteroposterior and oblique projections. This patient also has penoscrotal hypospadias and an incompletely descended right testicle.

Fig. 3. Case 11. These anteroposterior and lateral views show a dilated utricle after injection. Perineal hypospadias and bilateral inguinal cryptorchidism are also present.

Fig. 4. Case 13. A catheter passed into the sinus pocularis has traversed the vagina and entered the cervix uteri. Injection of radio-opaque salt has filled the vagina and the uterus. The contrast substance has entered the vas deferens through the right uterine cornu, visualized the epididymis, and extravasated into the tunica vaginalis. The arrow lies over the inguinal testicle. The bowel, containing barium, outlines the upper limit of the bladder, which is filled with water. There is also spillage of contrast medium onto the table outlining the natal cleft, thus producing a linear artefact in the bladder region.

tour was somewhat feminine. The facial hair was downy. The escutcheon was feminine, but the mons veneris was not developed. His voice was high-pitched. Large breasts with little glandular tissue had begun their development at the age of 12 years. Erections were infrequent and there had never been any discharge of semen. He was psychometrically masculine. The penis was 5 centimeters long. The urethra opened behind a bifid scrotum, and marked chordee was present. The left testicle was fully descended but pubescent in size, while the still smaller right testicle was palpable at the external ring. Epididymides were clearly identified. The prostate was ⅓ to ½ normal size. Urinary 17-ketosteroid excretion gave normal male values. Urinary gonadotropin estimation gave constant values of from 18 to 21 mouse units, a figure well within the range for normal men. The urethra was endoscopically masculine with visible secretion expressible from the prostatic ducts. Ejaculatory ducts were not identified. The utricle measured 2.0 by 2.5 by 1.3 centimeters.

Case 13. W.I. (Fig. 4). This boy was examined November 5, 1943, at the age of 3 years. He had two normal sisters and 2 normal brothers. His penis was small with marked chordee. The urethral meatus was in the perineum. The scrotum was cleft and was also deficient on the left. The right testicle was palpable at the external ring and its identity was proved

Fig. 5. Case 14. Injection through the vaginal orifice in the urogenital sinus has visualized the vagina, uterus, and uterine tubes. This patient possesses small pelvic testes. There are no ovaries.

by biopsy. The left gonad was absent, but a poorly developed left epididymis was found in the pelvis. An infantile bipartite uterus in communication with a vagina entering the posterior urethra just proximal to the external sphincter was demonstrated by x-ray examination and by laparotomy. The right vas deferens communicated with the uterus. The left vas was incomplete and blind. Uterine tubes and seminal vesicles were not identified. The posterior urethra felt slightly thickened on rectourethral palpation, but a prostate was not certainly identifiable. Laparotomy was performed on this patient for determination of the nature of the left gonad. The vagina, first demonstrable only by x-ray examination, was examined directly with the cystoscope 3 years later, finding a single external os. Following a urethroplasty and perineal urethrotomy with catheter drainage in 1946, the patient developed a febrile infection caused by accumulation of infected urine and pus in the vagina. This infection was successfully treated by endoscopic lavage.

Case 14. M.H. (Fig. 5). This young man was examined May 16, 1945, at the age of 20 years. He had 3 normal brothers and 2 normal sisters. He had been brought up as a girl, but the bodily contour, breasts, and voice were masculine. His facial hair required shaving thrice weekly. He had never menstruated. Psychometric tests gave strongly masculine findings. The penis was markedly incurvated and measured 7 centimeters.. Laparotomy disclosed atrophic pelvic testes and epididymides. The nature of the gonads was proved by biopsy. No vasa, seminal vesicles, or prostate could be found. A small uterus and uterine tubes were present. The vagina entered the urethra distal to the external sphincter, forming a short persistent urogenital sinus opening in the perineum. The scrotum was undeveloped and resembled labia majora. No urethral glands or verumontanum were demonstrable endoscopically. Determination of the 24 hour urinary 17 ketosteroid excretion gave values of 13.6 for the total and 8.8 for the ketonic fraction, figures which are borderline between the average findings for males or females.

Exploratory laparotomy was performed for determination of gonadal sex. Later the patient's legal sex was changed to male, and plastic procedures on the penis were performed.

DISCUSSION OF FINDINGS

Anatomically these 14 individuals may be divided into three groups. In group I (Fig. 6), penile hypospadias is the only departure from normal. In group II (Fig. 7), penoscrotal or perineal hypospadias is present with increasing degrees of chordee and diminution of the size of the penis. Anomalies of testicular descent and size are frequent, and the prostate may be poorly developed. The normal prostatic utricle is replaced by a rudimentary vagina entering the urethra at the verumontanum, which is frequently abnormal and sometimes occupies a position caudad to the normal. A uterus and uterine tubes are not demonstrable. The dilated utricle is normally empty, and its thin walls are not noticeable on palpation of the prostate. On urethroscopy, the utricular orifice is larger than normal and sometimes surrounded by hymen-like flaps. On catheterization of the orifice and distention of the utricle with fluid, a soft pyriform or ovoid mass lying usually a little to the right or left of the midline is easily

felt extending upward from the midportion of the prostate between the genitourinary tract and the rectum (Figs. 1, 2, 3). After withdrawing the catheter, the organ readily empties itself spontaneously. In group III (Fig. 8), the external genitalia closely resemble these of the female. The testicles are incompletely descended. The prostate, seminal vesicles, and vasa deferentia are poorly developed or absent, and a rudimentary uterus is present with the vagina communicating with the posterior urethra or uniting with the urethra distal to the external urinary sphincter to form a persistent urogenital sinus. The uterovaginal tract may be demonstrated by x-ray examination (Figs. 4, 5) or by direct endoscopy.

Except in Case 13, where the vagina became temporarily infected during a period of urethral catheter drainage, the 10 patients in this series possessing abnormal muellerian remnants have shown no signs of urinary tract obstruction or infection, nor have they complained of pain or other symptoms attributable to these anomalies. In no case has surgical removal of the vagina or uterus been considered necessary.

These young men and boys appear masculine in behavior and temperament and generally in physique, although evidences of mild to moderate hypogonadism are present in Cases 8, 11, 12, and 14. Of possible etiological significance in a negative sense is the absence of a family history of urogenital anomalies and the relationship of 13 normal brothers and 9 normal sisters to the group as a whole. Extraurogenital anomalies are infrequent.

DISCUSSION OF THE SIGNIFICANCE OF DILATATION OF THE UTRICLE

The association of any other genital anomalies with dilatation of the prostatic utricle is by no means uniform, nor is the condition always congenital. Several possible causes are to be considered: (1) inflammation, (2) neoplasia, (3) local developmental errors, and (4) intersexual development of the embryo.

Springer in 600 male autopsies found 3 utricular cysts in adults and one in a child. These cysts did not communicate with the urethra. Because of the finding of associated inflammation of verumontanum and prostate, he concluded that the cystic dilatation was secondary to inflammatory closure of the utricular orifice. Michailow, by endoscopy, and von Gaza, by surgical exposure, observed and treated utricular cysts which they felt on clinical grounds were inflammatory. R. A. Moore (32) in 678 autopsy specimens found 7 instances of cystic dilatation of the utricle but was unable to determine whether they were congenital or the result of inflammation.

At least 5 cases of massive retrovesical cysts apparently resulting from a benign cystadenomatous process in the utricle or a nearby muellerian duct rest have been reported (2, 8, 11, 18, 36).

Several possible local deviations from normal development are capable of causing utricular enlargement. Englisch, on the basis of autopsy studies, suggested that cystic dilatation of the utricle may arise from valve formation or fusion of the fetal mucous membrane at the point where the muellerian ducts enter the urogenital sinus. Boshamer in a clinical study of 4 adults with utricular cysts within the verumontanum not communicating with the urethra concluded that these cysts arose from a purely local developmental error because of the absence of signs of inflammation and of associated congenital defects. In certain mammals, particularly in ruminants, the utricle is normally a small cyst distinct from the urethra (22, 38). Siddiqi has shown in the ground squirrel that the growing muellerian ducts of the male embryo never reach the urogenital sinus. In the adult male of this species, the prostatic utricle is either absent or present as a small rounded structure which does not communicate with the urethra. Whether this is the mechanism of development of the normal closed utricle of cattle is not known; nor is there proof that analogous incomplete growth of the caudal ends of the muellerian ducts occurs in the human. However, an atavistic change of this nature provides a ready explanation for isolated congenital cysts of the utricle. Squamous metaplasia of the epithelium of the prostatic urethra and utricle in response to maternal estrogen during the latter months of pregnancy has been shown to occur in the human male fetus. When this epithelium desqua-

mates it frequently chokes the cavity of the utricle causing dilatation (5).

Although inflammation, neoplasia, isolated developmental errors, and physiologic epithelial metaplasia account for many instances of enlargement of the utricle, the findings in the subjects of this study are best explained on the basis of a feminization of the male embryo. Male pseudohermaphroditism as seen in Case 14 presents a striking example of feminization. The less obvious utricular enlargement with penoscrotal hypospadias becomes significant as an intersexual phenomenon when its relationship to the associated genital anomalies is considered from the embryologic standpoint.

A corollary to the theory of an intersexual type of development for this kind of utricular anomaly is that hypospadias also has a similar etiology. This view was supported by Felix, but Young (46) felt that except in the pseudovaginal type of hypospadias, the defect could be explained simply as the result of arrested development. The present study, although based upon a small number of cases, has uniformly demonstrated utricular enlargement in penoscrotal and perineal hypospadias. The only difficulty in explaining penile hypospadias on the basis of a simple developmental error is the lack of a satisfactory explanation for the chordee. If feminization of the embryo is assumed to occur, this difficulty is overcome, and penile hypospadias may be considered as a minimal degree of intersexual development.

Although Crew was able to correlate the changes in the external genitalia, gonads, and gonaducts of intersexual goats and pigs according to the degree of deviation from the normal, studies in the human have been lacking. Few cases of enlargement of the utricle in association with hypospadias are reported in the literature (1, 27, 30, 45). This is not surprising since the persistent muellerian structures rarely cause symptoms, and routine endoscopic examination is not generally practiced in hypospadias. Actually, reference to the presence of a definitive uterus in males with perineal hypospadias is encountered more frequently because the severity of the external deformity leads to surgical exploration (6, 9, 33, 45).

The freemartin of cattle and the congenital adrenogenital syndrome in the human suggest that masculinization of the female fetus by hormonal action sometimes occurs. Whether feminization of a gonadal male fetus takes place on a genic or an endocrine basis is debatable and cannot be settled here (see Witschi, C. R. Moore, and Greene, 15). However, treatment of pregnant rats with estrogen has shown that in this particular form of feminization of the male embryo, the changes produced are hypospadias, high testes, stimulation of the female ducts, and inhibition of the male ducts and prostate, changes similar to those observed in the human (16). While there are instances of a well differentiated uterovaginal tract in association with a normal penis and undescended testicles (34, 42) and also instances of large undifferentiated muellerian remnants in men with normal external genitalia (19, 20, 25), a combination of anomalies of both the internal and external genitalia is far more frequently observed.

In the human embryo of 6 weeks, the primordia of the genitalia are present in asexual form consisting of abdominal gonads, the genital tubercle, the wolffian ducts, and the developing muellerian ducts. In the male embryo of 8 weeks, the gonad is distinguishable as a testis, and the wolffian and muellerian ducts have established communication with the urogenital sinus at Mueller's hillock, which remains in the adult as the verumontanum. The wolffian system develops rapidly. The mesonephric tubules unite with the tubules of the testis and the mesonephric duct forms primitive seminal vesicles at 10 weeks. During the period between 8 and 10 weeks, the muellerian ducts undergo a brief period of incomplete proliferation without ever forming a definitive uterus or oviducts and begin to degenerate at 10 weeks. This degenerative process rapidly goes to completion leaving a remnant of the cranial end of each duct as the appendix testis and a remnant of the fused caudal ends as the prostatic utricle.[1] During

[1]Vilas has presented excellent evidence that the epithelium of the human prostatic utricle is all derived from the urogenital sinus contrary to the more generally accepted view that the organ is entirely of muellerian duct origin. In either case, the utricle, at its inception, arises from the growth of the muellerian ducts into the urogenital sinus.

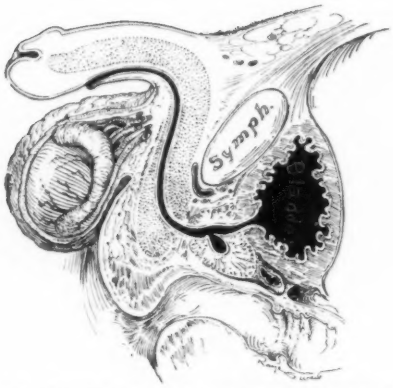

Fig. 6. Group I. Penile hypospadias is the only abnormality present. The testicle, prostate, seminal vesicle, and utricle are normal. This constitutes a minimal degree of feminization.

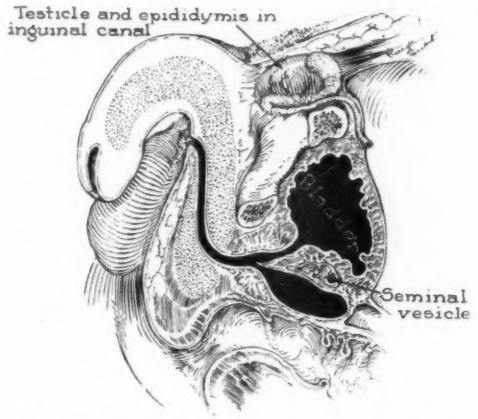

Fig. 7. Group II. There is a penoscrotal hypospadias. The testicle is incompletely descended. The penis, prostate, and seminal vesicle are smaller than normal. The utricle is enlarged. Here, feminization is more marked.

the period of from 6 to 10 weeks, the primitive phallus of the male enlarges, and the urogenital sinus, by a process of folding and fusion of the urethral groove from behind forwards, begins the formation of the urethra which is not complete until the 14th week. During the same period, the development of the scrotal swellings, the gubernaculum, and the formation of the processus vaginalis prepare the field for the descent of the testis. These changes proceed in a co-ordinated manner as the effect of a masculinizing influence upon the undifferentiated primordia. These same primordia under a feminizing influence in the normal gonadal female go through comparable changes in the opposite direction to form the homologous sexual organs. Whether these sex-determining influences are genic or endocrine in nature is as yet undetermined (15, 31). In the male embryo, should a feminizing influence or its equivalent, a deficiency of masculinizing influence, occur during the critical period of development, it would bring about associated intersexual changes. The extent of these changes is dependent upon the strength and duration of the feminizing influence and the time of the onset of its action. The penis and urethra, going through a longer period of definitive development, are most easily disturbed. Factors preparing the way for testicular descent appear to be somewhat less sensitive. The gonaducts undergo rapid definitive development in an earlier and shorter period. They are altered only by a more profound influence which if sufficiently strong may bring about extreme inhibition of the wolffian ducts and normal female differentiation of the muellerian ducts. Crew, interpreting the anatomical gradation of intersexual-

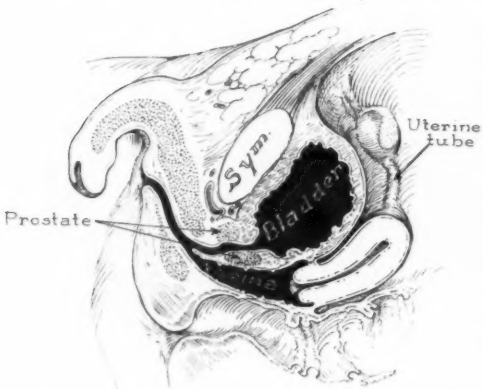

Fig. 8. Group III. The penis resembles a large clitoris. The urethral meatus is perineal. An atrophic testis with a rudimentary epididymis lies in contact with the uterine tube in the pelvis. A well developed uterus and vagina are present. The prostate is underdeveloped and seminal vesicles and vasa are absent. Feminization is extreme.

ity in the pig, suggested that a minimal masculinizing stimulus is necessary for normal sexual differentiation. Slight deficiency in this influence in time or degree brings about minor abnormalities affecting the external genitalia only; greater deficiency produces more marked alteration of the external genitalia plus incomplete muellerian duct recession; still greater deficiency causes pseudohermaphroditic abnormalities of the external genitalia, differentiation of the uterovaginal tract, and incomplete wolffian duct development. Similar gradations of feminization have been produced experimentally in newborn rats by estrogen treatment of the mother during pregnancy (16). The human subjects of the present study (Table I) also may be classified into similar groups: group I, penile hypospadias; group II, penoscrotal or perineal hypospadias, anomalies of testicular descent, dilatation of the prostatic utricle; group III, the same as group II plus differentiation of the uterovaginal tract, absence of the seminal vesicles, and incomplete development of the vasa deferentia (Figs. 6, 7, 8).

CLINICAL SIGNIFICANCE OF DILATATION OF THE PROSTATIC UTRICLE

Individuals with abnormally large utricles in free communication with the urethra rarely exhibit signs or symptoms of disease on this basis. These organs normally remain collapsed and when filled artificially with fluid rapidly empty themselves. Occasionally they may become distended and infected spontaneously or cause obstruction (7, 27). In the course of the operative treatment for hypospadias, serious infection may occur (Middleton; Case 13 of this series). Endoscopy and radiographic exploration of the utricle is of little value in the diagnosis of sex. The demonstration of a vagina or a uterus is not proof of gonadal femaleness. Should a well developed uterus be demonstrated, ovaries are most likely present, but if only a large utricle without evidence of uterus is present or if vasa deferentia are visualized, the gonads are probably testes. The site of vaginourethral communication is also a differential point determinable by endoscopy. Entrance of the vagina into the posterior urethra is a less feminine characteristic than communication between the vagina and urethra distal to the external urinary sphincter (21, 33). While endoscopic and radiographic findings may add to other clinical and laboratory evidence and aid in forming an opinion of the gonadal sex, they are not in themselves conclusive.

The discovery of utricular enlargement in hypospadias and the implication that these anomalies represent an intersexual type of development indicate the advisability of studying these individuals clinically as a whole organism rather than as the victims of an isolated fusion defect.

SUMMARY AND CONCLUSIONS

1. An unselected group of 14 males with hypospadias has been studied endoscopically and radiographically for remnants of the caudal ends of the muellerian ducts.

2. In penile hypospadias, the utricle is normal. In penoscrotal and perineal hypospadias, the utricle is markedly enlarged and may communicate with a well developed uterus.

3. The findings are presented as evidence for an intersexual type of development rather than a purely local developmental error as the cause of these anomalies.

4. Other causes of utricular dilatation or enlargement are discussed.

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ONE STAGE PHARYNGEAL DIVERTICULECTOMY

Improved Technique and Analysis of 186 Cases

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IN 1936 the senior author (2) reported a series of 76 personal cases of pulsion pharyngeal diverticulum in which he used the combined one stage method. The term "combined" refers to the simultaneous teamwork of surgeon and esophagoscopist throughout the entire operation. During the past 10 years his series has increased to 186 and the operative technique has undergone certain modifications. Our purpose is to analyze this larger series and to describe the present operative technique.

INCIDENCE

During the 5 year period from 1941 to 1945, the approximate incidence of pulsion pharyngeal diverticulum among total admissions at Jefferson Hospital was 1 in 1,400, among total operations 1 in 800, and among total esophagoscopic examinations 1 in 30. No cases were observed in the colored race. The age extremes were 37 to 83 years, the average age being 60 years. Males comprised 78 per cent and females 22 per cent (Chart 1). No cases were encountered before the fourth decade, and 82 per cent occurred during and after the sixth decade.

ETIOLOGY

It is now generally accepted that a pulsion diverticulum is caused by the intrapharyngeal pressure acting, during deglutition, from within outward upon a weak area in the muscular wall. Uncertainty exists as to whether the vulnerability is due to the normal penetration by nerves, blood vessels, and lymphatics, congenital muscular defect, neuromuscular incoordination or a combination of these.

PATHOLOGY

Although it is theoretically possible for a diverticulum to arise from any portion of the pharynx, in our experience all but 2 originated from the left lateral wall between the lowermost fibers of the inferior constrictor muscle and the upper border of the cricopharyngeus. On the other hand, the esophagoscopist reported the orifice of the sac approximately in the midline posteriorly in 60 per cent of the cases (Table I). This apparent discrepancy is caused by the fact that the esophagoscopist makes his observation while the pharyngeal wall is in a state of torsion produced by descent of the enlarging sac in the retropharyngeal space. The surgeon, however, makes his observation when the torsion defect has been corrected by his dissection. The largest pharyngeal opening encountered was 4 centimeters in diameter. In 2 instances the fundus of the sac was bilocular but there was only 1 opening into the pharynx. In many instances the fundus of the sac extended well into the superior mediastinum (Fig. 1). Multiple pharyngeal diverticula were not encountered, but 3 cases were associated with traction esophageal diverticula and one with a duodenal diverticulum.

The diverticula varied in size from 1 by 1 by 0.6 centimeters to 8 by 3.5 by 2 centimeters, but the majority, namely 43 per cent, were between 2.5 and 5 centimeters in their greatest diameter, and were classified as medium sized (Table I). In 77 per cent of the cases the esophagoscopist reported inflammation of the mucosal lining, and in 16 per cent it was severe. This undoubtedly accounts for the adherence to surrounding tissues so commonly noted at operation.

Histologically, the diverticulum consists of a fibrous tissue wall lined by stratified squamous epithelium. In the wall there are usually dilated blood vessels, small foci of inflammatory cells, and occasionally a few scattered striated muscle fibers. Malignant change was not encountered in this series.

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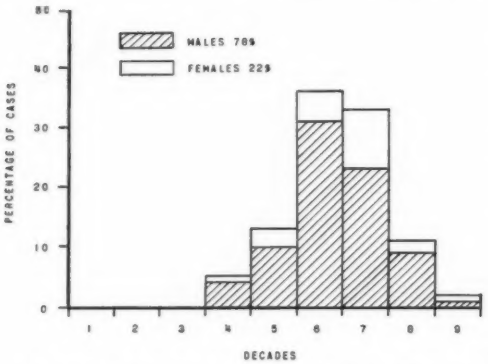

Chart 1. Distribution of cases according to age group and sex.

DIAGNOSIS

The symptoms of pharyngeal diverticulum, listed in Table II, varied in duration from a few weeks to 40 years, the average being 4½ years. Of these, only 1, namely noisy deglutition, deserves special mention, since it is seldom encountered as a symptom of other lesions producing dysphagia. It occurs when the sac contains fluid and air during swallowing. During this act a gurgling sensation is usually palpable at the site of the sac. Pressure on the neck over the sac will sometimes express its contents into the patient's mouth. In other cases physical signs may be altogether lacking.

While the clinical picture of pharyngeal diverticulum is as a rule typical, errors in diagnosis do occur. Occasionally we have had to differentiate between pharyngeal diverticulum, cicatricial stenosis, and carcinoma of the cervical esophagus. Although this was accomplished by the roentgenologist alone in the majority of cases, it was often found necessary to have the esophagoscopist make the final conclusive study. Therefore, in all lesions of the pharynx and esophagus we recommend both roentgenologic and esophagoscopic studies.

TABLE I.—PATHOLOGIC DATA

	Per cent
Location of sac (Esophagoscopist's report)	
Left	24
Right	16
Midline	60
Size of sac (Pathologist's report)	
Small (up to 2 cm.)	30
Medium (2.5 to 5 cm.)	43
Large (over 5 cm.)	27
Inflammation (Esophagoscopist's report)	
Mild	61
Severe	16
Absent or not mentioned	23

TABLE II.—SYMPTOMS

Common	Per cent	Less common	Per cent
Dysphagia	86	Expectoration of mucus	11
Regurgitation	83	Fullness in throat	10
Noisy deglutition	64	Choking sensation	10
Weight loss	44	Soreness in neck	7
Cough	35	Hoarseness	2

TREATMENT

Preoperative. In this series, the average length of time required to prepare patients for the operation was 5 days. During this period, therapy is directed toward correction of nutritional deficiencies such as secondary anemia, hypoproteinemia, and avitaminosis by dietary and parenteral methods. In a few instances tube feeding was necessary and in 9 cases preliminary gastrostomy. The latter has been per-

TABLE III.—CONCOMITANT DISEASES AND COMPLICATIONS IN LAST 100 CASES

Preoperative	Number or per cent	Postoperative	Number or per cent
Cardiovascular (Auricular fibrillation, heart block, hypertension)	7	Temporary vocal cord paralysis	9
		Wound infection	4
		Simple	3
		With fistula	1
Pulmonary (Tuberculosis, fibrosis, asthma)	6	Recurrence	1
Urinary retention	3	Parotitis	2
		With recovery	1
		With uremia and death	1
Traction esophageal diverticula	3		
Miscellaneous (Left vocal cord paralysis, diaphragmatic hernia, duodenal ulcer and diverticulum, papilloma of larynx, diabetes, severe inanition requiring gastrostomy)	6	Atelectasis	1
		Pneumonia and death	1
		Auricular fibrillation	1
		Coronary occlusion and death	1

formed only once in the last 137 cases. Concomitant diseases (Table III) require special attention and often prolong the preoperative period.

In order to decrease inflammatory reaction in the sac wall, patients are taught to cleanse and empty the sac after each meal by swallowing water, compressing the neck at the area of the sac, and leaning forward to let it drain out.

Operative. The salient features of the combined one stage procedure are as follows: first, cleansing and emptying of the sac through the esophagoscope; second, maintenance of the normal anatomic position of pharynx and upper esophagus by keeping the esophagoscope in the esophagus during ligation of the sac neck and transplantation of its stump, as well as during the entire period of pharyngeal repair. The restoration of normal anatomic alignment, which is assured by this method, favors normal function after healing has occurred. For this operation we have found open drop ether anesthesia to be the most satisfactory.

a. Esophagoscopic technique. It is important to empty the contents of the pouch, since it is common to find secretion and not infrequently masses of food. These should be removed to prevent overflow into the trachea when the pouch is manipulated.

Fig. 1. Roentgenogram of unusually large pulsion pharyngeal diverticulum, showing fundus of sac extending well into the superior mediastinum.

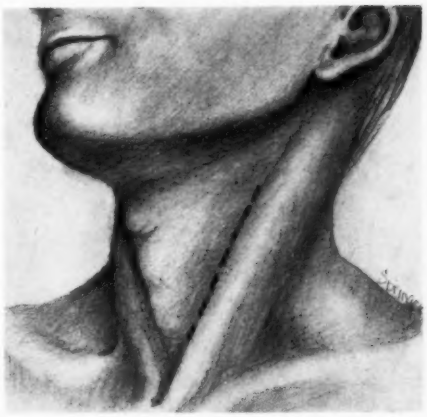

Fig. 2. Skin incision for pharyngeal diverticulectomy.

Identification of the diverticulum by the surgeon can be accomplished promptly if the tip of the esophagoscope is introduced into the pouch so that it can be palpated through the incision and the sac transilluminated. After it is clearly identified and partially separated, further esophagoscopic assistance is unnecessary until ligation of the neck of the pouch. The esophagoscope is then introduced into the subdiverticular esophagus, guided by an olive-tipped bougie passed over a thread swallowed the day prior to operation. This avoids the occurrence of esophageal stenosis which might ensue if too much of the pharyngeal and upper esophageal walls are removed. In addition, it also aids the surgeon in removal of the entire pouch.

At the conclusion of operation, a feeding tube is inserted through the esophagoscope into the lower esophagus. The esophagoscope is then removed without disturbing the feeding tube, the proximal end of which is withdrawn through the nose.

b. Surgical technique. An incision is made along the anterior border of the left sternocleidomastoid muscle from 1 inch above the sternum to the level of the hyoid bone (Fig. 2), passing through the skin, platysma, and deep fascia, exposing the anterior belly of the omohyoid muscle. The latter may be severed or

Fig. 3. Steps in excision of pharyngeal diverticulum: a, identification of sac by esophagoscopic transillumination; b, freeing of sac neck to submucous coat; c, ligation of sac neck, with esophagoscope in place; d, ligation completed; e, severance of sac neck between ligature and clamp; f, sterilization of stump.

retracted. The diverticulum is then approached by incising the pretracheal fascia near its lateral margin, retracting the contents of the carotid sheath laterally and the thyroid gland and trachea medially. It is sometimes necessary to divide the inferior thyroid vessels for better exposure.

The fundus of the sac, which is now rotated into the wound and transilluminated by the esophagoscopist (Fig. 3a) is grasped with intestinal forceps and drawn upward and outward, after which the esophagoscope is withdrawn from the sac. The diverticulum is then entirely freed to its junction point with the pharynx (Fig. 3b). Care must be exercised to free all muscle fibers from its neck, exposing the submucous coat. This will assure stability of the ligature to be placed subsequently by minimizing the amount of tissue included in it. The neck of even the largest diverticulum is seldom more than 1½ centimeters in diameter. A neck larger than this usually indicates incomplete dissection.

A moist sponge is packed in the lower pole of the wound, to safeguard the mediastinum from contamination. Then, with the esophagoscope in the esophagus, a transfixion suture of No. 1 chromic catgut is placed in the sac neck at its junction with the pharynx and the ends left long (Fig. 3, c and d). An additional braided silk tie is used for reinforcement when the sac neck is edematous or unusually large. After clamping a hemostat across the sac neck just distal to the ligature, the sac is severed between the ligature and hemostat (Fig. 3e). Phenol and alcohol are applied to the stump (Fig. 3f), following which the protective sponge previously placed is removed. The long ends

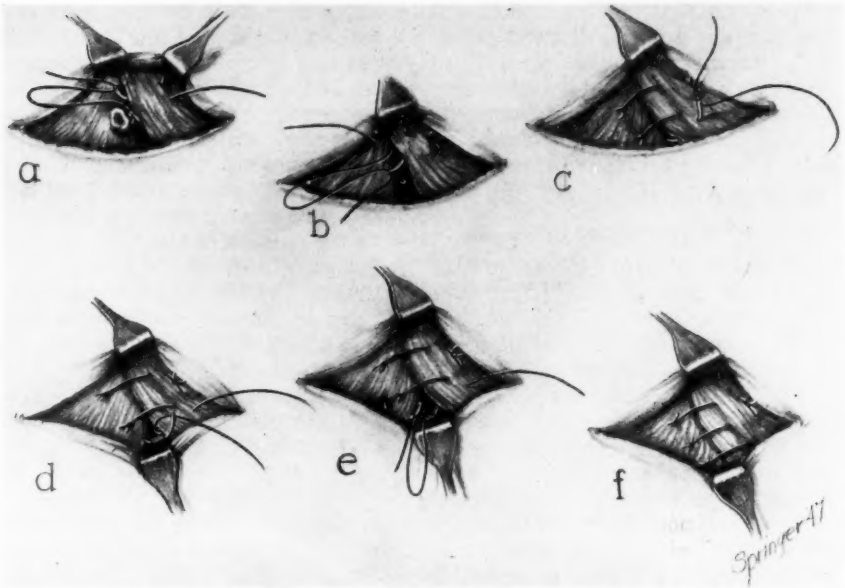

Fig. 4. Steps in repair of pharyngeal wall, following excision of diverticulum: a, transplantation of stump beneath inferior constrictor muscle; b, approximation of cricopharyngeus to inferior constrictor muscle; c, d, and e, anchoring of posterior suture to prevertebral fascia; f, pharyngeal repair completed.

of the transfixion suture are used, and the stump is transplanted upward beneath the inferior constrictor muscle (Fig. 4a). The muscular defect in the pharyngeal wall is now corrected by approximating the upper margin of the cricopharyngeus to the lower margin of the inferior constrictor with interrupted No. 1 chromic sutures spaced about 1 centimeter apart (Fig. 4, b and c). The posterior portion of the suture line which overlies the retropharyngeal space is anchored to the prevertebral fascia (Fig. 4, d, e, and f). This important stitch obliterates the retropharyngeal space at this point, erects a barrier against descending infection into the mediastinum by way of the retropharyngeal space, and reinforces the posterior portion of the suture line. The incision is closed in layers around a small Penrose drain placed in the lower pole of the wound. The average operating time for this procedure was 45 minutes.

Postoperative. The usual hospital stay after operation is 21 days, but only during the first 5 to 7 days is the patient confined to bed. The wound is treated as in any clean case and the Penrose drain is removed on the seventh day. A concentrated liquid diet is administered through the indwelling nasal tube in increasing amounts according to the plan in Table IV. In order to maintain nutritional and fluid

TABLE IV.—POSTOPERATIVE FEEDING SCHEDULE FOR AVERAGE CASE

Day	Nasal tube feedings		Time interval between feedings
	Water ounces	Concentrated liquids* ounces	hours
1	½	1	1
2	1	2	1
3	1	3	1
4	1	4	1
5	1	5	1½
6–17	1	6	2
18–19	Full liquid diet		
20	Soft Diet		
After 6 weeks any type of food is allowed.			

*The composition is the same as for gastrostomy feedings.

balance during the first few days additional fluids and vitamins are administered parenterally. The nasal tube is left in place for 18 days, acting as a splint during the healing process. A day or two after its removal, roentgenologic examination of swallowing function is done. By this time the operative site is healed and a soft diet readily tolerated.

COMPLICATIONS

Complications occurring in the early cases of this series have been described in previous reports (1, 2). Those occurring in the last 100 cases are listed in Table III. The most frequently observed complication was unilateral vocal cord paralysis, which was temporary in all instances. The normal location of the recurrent nerve at the lower border of the inferior constrictor muscle is a vulnerable one. In 1 instance paralysis of the left vocal cord was present before operation. Injury to this nerve can only be minimized by exercising care during retraction of the thyroid gland and trachea, freeing of the sac, and repair of the pharyngeal wall.

Only 1 of the wound infections did not respond readily to chemotherapy and local conservative measures. In this instance a fistula persisted for 10 weeks but then remained healed. Mediastinitis was not encountered in the entire series of 186 cases.

In several instances, postoperative roentgenologic examination revealed retention of a speck of barium at the operative site. These dimples were not associated with symptoms and the patients were considered cured. One patient, however, was well for 6 months, but then had a mild recurrence of symptoms. Roentgenologic and esophagoscopic examinations revealed a pharyngeal sac which was deemed too small to warrant reoperation at that time. She was advised to return for follow-up 6 months later but failed to do so.

In the entire series of 186 cases there were 5 deaths or a mortality of approximately 3 per cent. The causes were pneumonia in 2 instances, uremia in 1, uremia with parotitis in 1, and coronary occlusion in 1. It is therefore apparent that the mortality of one stage pharyngeal diverticulectomy is no greater than would be expected for any other major operation in this age group.

CONCLUSIONS

1. Combined surgical and esophagoscopic technique for the one stage removal of pulsion pharyngeal diverticulum, herein described, represents a sound anatomic and physiological approach to the treatment of this lesion.

2. Experience in 186 cases has shown this method to be safe and effective.

Since this paper was submitted for publication 4 additional patients have been operated upon with normal recovery.

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OSGOOD-SCHLATTER'S DISEASE

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A LARGE literature has accumulated on painful tibial tuberosities in the adolescent since attention was directed thereto by Osgood and Schlatter. The disorder is uncommon and save for a few notable exceptions (7, 8) reports have been based on very small series or even on single cases. The development of the tibial tuberosity is complex and an understanding of its normal anatomical features has been obscured by inaccurate descriptions. Moreover, indications are rarely present for operative interference. For these reasons it is not surprising that there should be widely varying interpretations of the pathological changes which take place in the presence of Osgood-Schlatter's disease.

THE ANATOMY OF THE TIBIAL TUBEROSITY

The tibial tuberosity has a proximal smooth (Fig. 1, *s*) and a distal rough part (Fig. 1, *r*). The proximal surface of the tuberosity is separated from the upper anterior surface of the tibia by a groove (Fig. 1, *g*) that begins at the upper medial corner of the tuberosity, extends to, and turns distally along the lateral side of the tubercle as far as the junction of the smooth and rough parts. This groove varies in depth from bone to bone but is constantly present.

The ligamentum patellae is inserted into the groove and into the smooth part; investigation has proved that this insertion is strongest in the groove and less so in the tibial tuberosity (3). The deep infrapatellar bursa is related to the tibia immediately proximal to the groove (Fig. 1, *h*); this bursal area may be poorly defined but in many cases stands actually to overshadow the tuberosity itself. The line of demarcation between the smooth and rough halves of the tuberosity lies obliquely like the groove, extending farther distally on the lateral side. This line of demarcation indicates the site of fusion which has taken place between the apophysis and diaphysis.

THE DEVELOPMENT OF THE TIBIAL TUBEROSITY

The conclusions in Table I are based on the examination of more than 100 x-ray films. Interpretation of roentgenograms depicting such a small area is made difficult by the marked variation in the films resulting from projections at slightly different angles. The observations are in agreement with those of Perrot who conducted a similar investigation. The development of one or more apophyseal[1] centers at the age of 11 years, their fusion with each other and with the epiphyseal tongue a few months later, and the closure of the apophyso-epiphyseal line at about 15 years of age are now fairly generally accepted. Development proceeds a little more rapidly in females.

THE RADIOLOGICAL APPEARANCES IN ADOLESCENT PAINFUL TIBIAL TUBEROSITY

Since 1940, 17 children seen at this hospital have been found to be suffering from the con-

[1]Apophysis; the term is used here to denote a part of the epiphysis which ossifies from a separate center or centers.

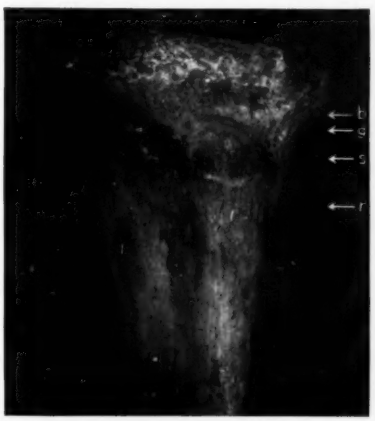

Fig. 1. Anatomy of tibial tuberosity. *s*, Proximal smooth and, *r*, distal rough part; *g*, groove; *b*, bursal area.

From the Wingfield Morris Orthopaedic Hospital.
Dr. Hughes is holder of travelling fellowship of the National Health and Medical Research Council, Australia.

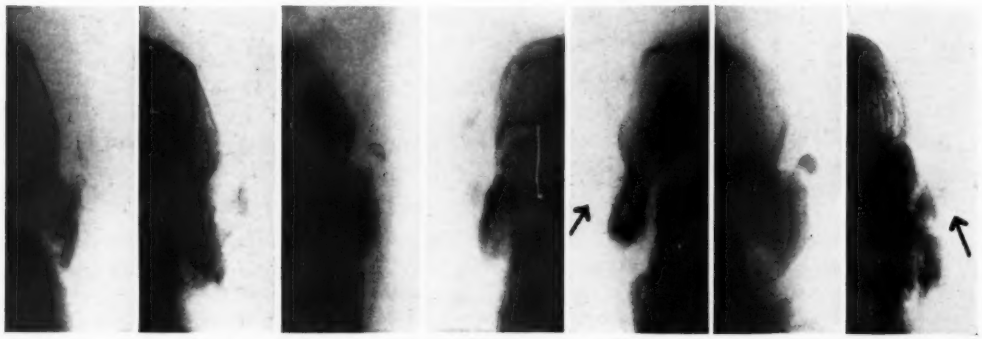

Fig. 2. Fig. 3. Fig. 4. Fig. 5. Fig. 6. Fig. 7. Fig. 8.

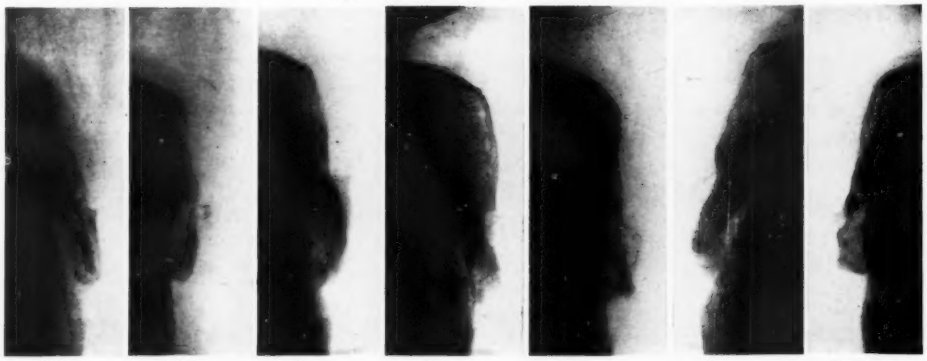

Fig. 9. Fig. 10. Fig. 11. Fig. 12. Fig. 13. Fig. 14. Fig. 15.

Fig. 2. Male, 14 years old.
Fig. 3. Female, 12 years old.
Fig. 4. Female, 13 years old.
Fig. 5. Female, 13 years old, right knee (see Fig. 11).
Fig. 6. Female, 12 years old.
Fig. 7. Female, 12 years old.
Fig. 8. Male, 12 years old.
Fig. 9. Female, 13 years old.
Fig. 10. Female, 11 years old.
Fig. 11. Female, 13 years old, left knee (see Fig. 5).
Fig. 12. Female, 14 years old, left knee (see Fig. 15).
Fig. 13. Female, 11 years old.
Fig. 14. Male, 15 years old.
Fig. 15. Female, 14 years old, right knee (see Fig. 12).

dition (3 with bilateral involvement.) The feature common in all the x-ray films is either ossification within, or enlargement of, the ligamentum patellae. The ossification may be found at the site of insertion into the tuberosity, in the ligament at a higher level, or at both these sites. The abnormal bone at the ligamentous insertion may be in the form of a linear ridge (Figs. 2 to 10), a plaque of bone (Figs. 11–16), or mottled and irregular ossification (Figs. 17–20). The ossification situated higher in the ligament may be linear or irregular and may be connected with the bone formation at the insertion by bridges of bone. In the one x-ray film which showed no ossification within the tendon (Fig. 21) there was demonstrated a kidney shaped opacity at the site of its insertion.

The epiphysis has united with the apophysis to form a continuous beak; indeed, this formation is to be expected since it was found in the normal films of this 12 to 14 year age period (Table I, and Fig. 33). The epiphyseal part of the beak is never primarily involved in pathological changes; the apophysis also usually escapes. It was found that in those cases in which a mottled irregular ossification is displayed at the site of insertion some osteoporo-

Fig. 16. Fig. 17. Fig. 18. Fig. 19. Fig. 20. Fig. 21.

Fig. 16. Male, 14 years old.
Fig. 17. Female, 12 years old, left knee (see Fig. 18).
Fig. 18. Female, 12 years old, right knee (see Fig. 17).
Fig. 19. Male, 15 years old.
Fig. 20. Male, 15 years old.
Fig. 21. Male, 14 years old.

sis of the underlying bone is also shown (Figs. 17 to 20); this rarefaction is localized to the surface of the apophysis.

THE PROGNOSIS IN ADOLESCENT PAINFUL TIBIAL TUBEROSITY

A small number of patients were re-examined at intervals varying from 1 to 9 years after the onset; 2 others, aged 26 and 34, respectively, sought advice for persistent recurrence of pain in the region of the tuberosity since adolescence. All these patients possessed a prominent tibial tuberosity (the photographs of the knees of 2 patients are reproduced in Figs. 22 and 23). The tuberosity in some cases was tender on palpation, and about half of the patients experienced pain in this region which was precipitated by exercise, by kneeling, or even by sitting on a chair. A radiological examination showed an enlargement of the tuberosity at the site of the insertion of the ligamentum patellae; frequently, a separate ossicle was present within the ligamentum; and an irregular buttress of bone tends to form just above the tuberosity, posterior to the tendon (Figs. 24 to 32).

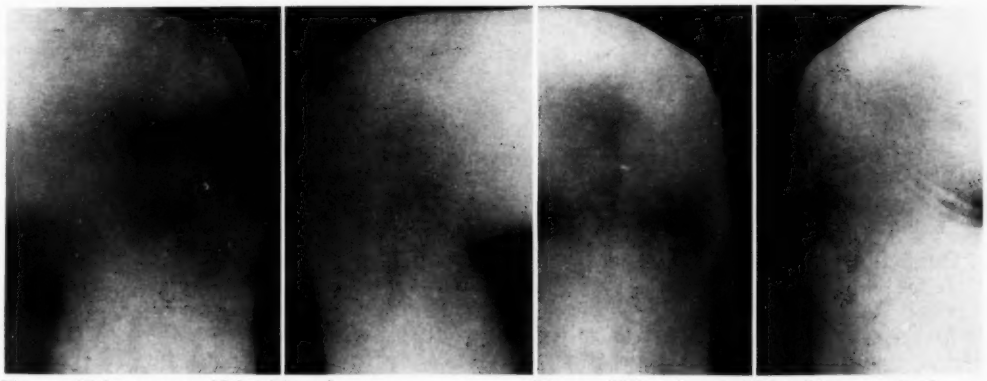

Fig. 22. Male, 15 years old (see Fig. 24).

Fig. 23. Male, 20 years old (see Figs. 27 and 28).

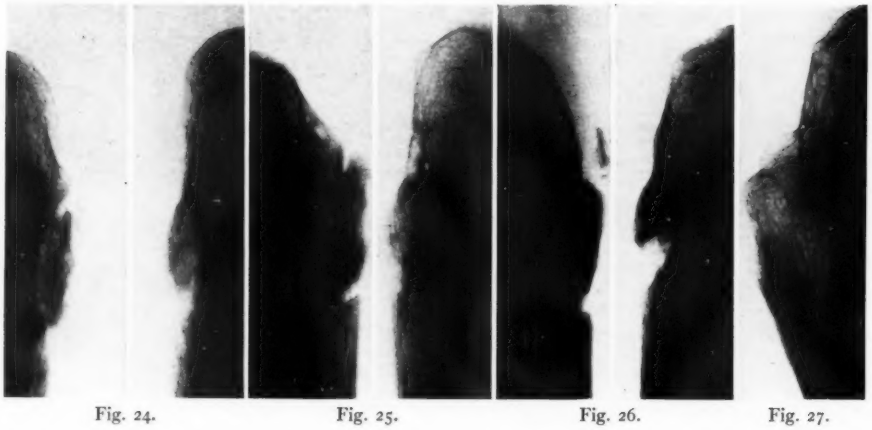

Fig. 24. Fig. 25. Fig. 26. Fig. 27.

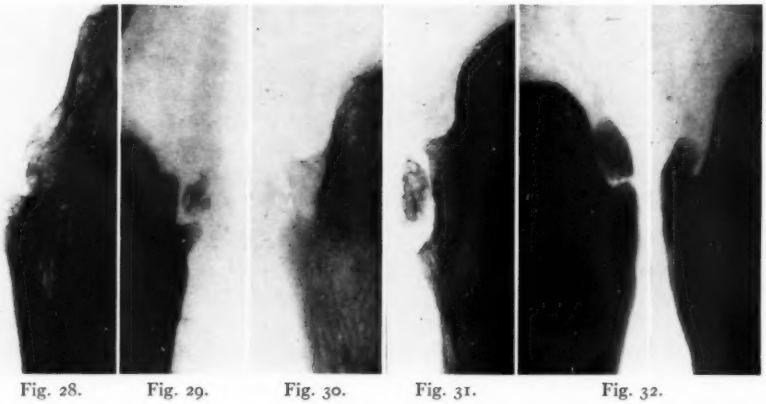

Fig. 28. Fig. 29. Fig. 30. Fig. 31. Fig. 32.

Fig. 24. Male, 15 years old. Same case as in Figure 2, unaffected knee shown.
Fig. 25. Female, 15 years old. Same case as in Figure 13, unaffected knee shown.
Fig. 26. Female, 13 years old. Same case as in Figure 3, unaffected knee shown.
Fig. 27. Male, 20 years old, left knee (see Fig. 28).
Fig. 28. Male, 20 years old, right knee (see Fig. 27).
Fig. 29. Female, 18 years old. Same as in Figure 10.
Fig. 30. Male, 34 years old.
Fig. 31. Male, 26 years old.
Fig. 32. Female, 17 years old. Same case as in Figure 17 and 18. Left and right knees.

DISCUSSION

A knowledge of the normal anatomical and radiological features of the tibial tuberosity in the varying stages of its development is indispensable if the true nature of Osgood-Schlatter's disease is to be understood.

The investigation recorded here shows clearly that the clinical features of this affection are almost certainly due to a pathological change primarily within the ligamentum patellae rather than in the apophysis. The ossification at the site of insertion is readily accounted for by the partial tearing of the ligamentum from the bone. The insertion of this tendon into the smooth portion of the tuberosity is not as firm as it is into the groove (3), and this may well be the cause of the involvement of the former and the sparing of the latter as seen in most of the early x-ray films. The ossification higher in the ligament may be due to an extension of

TABLE I.—THE DEVELOPMENT OF THE TIBIAL TUBEROSITY.

Age group-years	Stage of development of tibia
0–6	The ossification of the epiphysis results in the formation of a disc at the proximal end of the tibial diaphysis. There is no extension yet to form the epiphyseal part of the tubercle. The diaphyseal or roughened half of the tuberosity may or may not be represented by a ledge.
6–8	The epiphysis increases slightly in depth in its anterior part. The diaphyseal ledge is more definite though it may be concealed by an oblique projection. The apophysis remains unossified
8–10	A small tongue of ossification appears from the anterior and inferior edge of the epiphysis. In some films there appears to be an extension of ossification from the diaphyseal ledge into the lower part of the apophysis but this appearance is due to the obliquity of the ledge
10–12	The tongue of ossification from the epiphysis continues to extend distally. The distal part of the epiphysis ossifies in most cases from one or more centers. This apophyseal ossification forms the prominent smooth part of the tubercle and joins the epiphyseal tongue at the site of the groove
12–14	The apophysis and epiphysis become continuous. The beak so formed varies very considerably in appearance as does its degree of separation from the diaphysis
14–16	The line of separation between the combined epiphysis and apophysis and the diaphysis is slowly obliterated. The oblique and vertical portions of this line appear to be the first to fuse, followed by fusion of the "beak" and diaphyseal ledge

this osteoblastic reaction or to metaplasia of fibroblasts. In either case it would appear that the initiating stimulus is injury to the ligament, direct or indirect.

This conception of Osgood-Schlatter's disease as a "tendinitis ossificans" is in full accordance with all the known facts. Children are affected at an age when osteoblastic activity of this area is at a maximum. The slightly earlier incidence in girls corresponds to their earlier development (Fig. 33). Injury may or may not be recalled but this is an age period when such recollection is difficult. Pain at rest and during exercise, a tender, enlarged tuberosity, the characteristic radiological features all receive an adequate explanation.

Trauma was believed by both Osgood and Schlatter to be the cause of the painful tuberosity, and this opinion is now regarded as correct. But its mechanism in the production of the condition has not been clearly understood. Some believe that it causes separation of the tongue-like epiphysis from the diaphysis, or even fractures the epiphyseal beak; others believe that the injury interferes with the blood supply and so causes an aseptic necrosis of the apophysis; while others again consider that

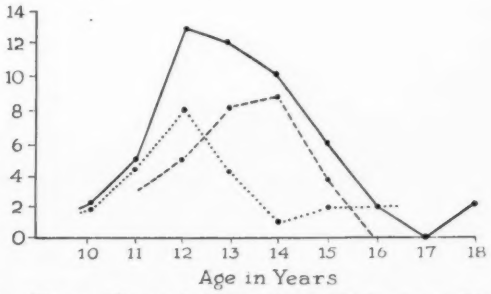

Fig. 33. The age incidence of 51 patients seen at this hospital, 1930–1946 inclusive, and diagnosed as suffering from Osgood-Schlatter's disease. Total, 51; females, 23; males, 28.

there is a disorganization of the apophyseal centers or actual avulsion of a fragment of bone. The finding by some authors that the first radiological sign of this disease is a thickening of the ligamentum patellae (1, 2, 7); the almost constant radiographic demonstration of opaque material within the ligament, as described here and as seen in x-ray films reproduced by others; the increase in density of this material in successive x-ray films, clearly seen in some of our cases as well as in those published by others, all favor the view that Osgood-Schlatter's disease is of the same pathology as myositis ossificans which occurs in the muscle and tendinous fibers of brachialis at the elbow.

With the great number of variations possible in the radiological appearances of the normal tuberosity, it is most hazardous to diagnose Osgood-Schlatter's disease from such appearances as increased densities, osteoporosis, partial separation, pitting, irregularities, and similar conditions. The appearance of fragmentation is a normal stage in the apophyseal development; Osgood-Schlatter's disease cannot be compared with osteochondritis of the hip where fragmentation is a radiological sign of disease. The only definite abnormality of the apophysis observed here was the osteoporosis of the surface at the site of insertion of the ligamentum; this was observed clearly in only 5 cases (Figs. 15, 17, 18, 19, 20) and its presence is accounted for by a reactive hyperemia at the site of the injury. A lack of clear definition of the tuberosity which is apparent

in some of the roentgenograms can be attributed to the presence of changes in the overlying soft tissues.

It may be concluded that there is the strongest evidence in support of the belief that Osgood-Schlatter's disease is primarily an intraligamentous rather than an epiphyseal condition.

SUMMARY

1. The normal anatomy of the tibial tuberosity and the insertion of the ligamentum patellae have been reviewed.

2. The development of the tuberosity has been traced radiologically.

3. From a study of the condition in 20 knees it is concluded that the essential lesion in Osgood-Schlatter's disease is a "tendinitis" rather than an "epiphysitis."

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BARTHOLIN CYST

A Simple Method for its Restoration to Function

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THE vulvovaginal gland (Bartholin) is a racemose gland lying beneath the labia minora. It secretes a clear, viscid fluid through its ostium which is located superficial to the hymen in the region of 5 and 7 o'clock. The purpose of the secretion is to lubricate the vulva. As with all glands, the amount of secretion varies from time to time but, generally speaking, the amount of secretion is indicative of the interest in mating.

Bartholin's gland may become diseased and be converted into a cystic formation. Should the cyst become secondarily infected an abscess may result. The latter is limited to the gland and its duct. It rarely extends to the adjacent tissues such as an infection by the streptococcus would produce.

Because of the location of the gland in the vulva, disease of this structure should not be interpreted as prima facie evidence of a venereal infection. The Micrococcus catarrhalis is frequently the invading organism in the simple cyst, and in the purulent involvement the culture is usually sterile and rarely shows the presence of the gonococcus.

The conversion of the small racemose gland and its duct into a large cyst or abscess suggests a mild infective process originating in or near the minute opening of the vulvovaginal gland, which through inflammatory changes occludes the opening of the duct (ostium). The rhythmic secretion of the gland blocked by the occlusion of the duct at its ostium distends the duct and converts it into an apparently large thin walled cystic mass. The patient may frequently detect a periodicity in the distention and regression in the size of the cyst; such a rhythm suggests that the gland has not been destroyed by pressure necrosis but that the secreting cells are responding to normal physiological processes.

It should be the objective of the gynecologist to conserve the function of the diseased gland because of its importance in the intelligent interpretation of waves of interest, monotony, or fatigue which are present in varying degrees during the process of mating. They are revealed to the male by the presence of lubrication or dryness of the vulva and should suggest a continuation of the mating process or a short period of rest which should be followed by another method of approach if the fullest mental and physical reaction is desired for the female.

The use of vaseline as a lubricant following the surgical removal of the diseased gland may prevent trauma due to dryness and friction but it does not encourage emotional interpretation. The sex act, unfortunately, frequently becomes a habit and the use of vaseline encourages the routine sex act which tends to become tiresome and fatiguing instead of being enjoyable and stimulating.

Sterility due to tubal spasticity frequently requires consultation with a psychiatrist. His treatment is enhanced by a normally functioning gland which tends to prevent tubal spasticity resulting from friction and trauma.

The restoration of the diseased gland to normal without surgical removal requires an intelligent interpretation of the pathological process responsible for the formation of the cyst as well as an accurate anatomical background. Casper Bartholin (1655-1738) of Copenhagen, Denmark, described the gland but it remained inaccurately described until Bern Gallaudet, of Columbia University, showed that the gland was a homologue of Cowper's gland and that it lay deep to the bulbocavernous muscle and the bulb in the deep compartment of the perineum, i.e., on the deep transverse perineal muscle. Being restrained by the superficial and deep layers of the uro-

Fig. 1. An incision has been made into the cyst close to its original ostium. A strip of iodoform gauze fills the cavity of the evacuated cyst.

Fig. 2. Appearance of the new ostium, 2 months after incision. Five replacements of the packing were required to effect the permanent ostium.

genital diaphragm (triangular ligament) it is impossible for the gland to dissect between the resistant layers to enlarge and become cystic. Instead, it is the duct of the gland which becomes distended as it traverses the loose connective tissues between the gland *per se* and its ostium. In the superficial perineal pouch, the loose tissues are readily distorted and the dilated cystic duct may cause considerable distortion of the bulb, bulbocavernous muscle, and the labia.

Microscopic study verifies the anatomical finding that the cyst is confined to the duct. Normally the epithelial lining of the Bartholin gland is of the columnar variety while that of the duct is transitional epithelium. The latter variety and even squamous epithelium lines the cavity of enucleated cysts. Careful examination of extensively dissected specimens may reveal a small nodule attached to the cyst which nodule is lined with columnar epithelium. It represents the gland proper.

The final picture is one in which the minute gland lying between the resistant layers of the urogenital diaphragm communicates with a greatly distended duct which distorts the labia and is adherent to the vulva at the site of its occluded ostium.

Careful surgical removal of the cyst usually results in a rupture of the cyst at its ostium which is in the region of 5 or 7 o'clock and at its attachment to the secreting diaphragm. As a rule the gland *per se* is not removed, but the scar tissue resulting from the operative procedure may completely occlude the gland and cause its atrophy.

The author was taught to assume that each case, more likely than not, was the result of a venereal infection and that complete enucleation was the treatment of choice. After being consulted by several patients whose complaint was dyspareunia following the bilateral enucleation of Bartholin's cysts, he was influenced by the anatomical position, microscopical study, and the frequency of negative cultural reports to change his form of treatment from that of complete excision of the cyst to that of ample drainage and the construction of a permanent ostium which would completely drain the diseased duct and permit the

remaining secretory cells to regenerate and function.

Twenty-five cases have been treated by incision close to the hymen in the region of the opening of the duct. The cavity of the cyst is then packed with iodoform gauze, which is removed and replaced biweekly for approximately 3 weeks. At the end of this time an opening admitting the blunt end of a pencil represents the newly constructed ostium. The packing prevents the small incision from agglutinating and permits epithelization of the new ostium with squamous epithelium. Ample drainage should permit the diseased gland to return to normal and require no further treatment, but occasionally the ostium may contract and necessitate dilatation with a blunt instrument. The restoration to normal is verified by the disappearance of the mass and the presence of a clear, viscid secretion in the region of the fossa navicularis.

COMMENTS

Drainage of the diseased duct is readily accomplished by infiltration with a local anesthetic and incision, either in the hospital or in the office depending on the type of patient to be treated. To facilitate packing, the edges of the incision should be held with clamps so that the collapsed cyst may not retract into the deeper tissues.

Since the treatment is usually performed in the office, confinement to bed is not required.

No case in which this method of treatment was carried out has been complicated by postoperative hemorrhage, either immediately following the incision or several days later. The author is familiar with several cases of severe postoperative hemorrhage following the surgical removal of the cyst which required transfusion, packing, and even resuturing before the bleeding could be controlled.

CONCLUSIONS

The so called cyst or abscess of Bartholin's gland actually consists of a dilatation of the duct of the gland.

The periodical swelling and recession of the cyst suggest occlusion of the ostium with intermittent drainage.

The swelling of the cyst suggests activity of the secreting cells which lie between the layers of the urogenital diaphragm.

The purpose of the incision and packing of the cyst cavity is to permit restoration of function by the construction of a patent ostium.

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RESULTS AND CAUSES OF FAILURE OF RADIATION THERAPY IN CARCINOMA OF THE CERVIX

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THE combined use of roentgen radiation externally and surface radium application internally has long been widely accepted as the method of choice for the treatment of cervical carcinoma. In recent years, however, this technique has been challenged and a number of other methods, including a return to radical surgery, have been strongly advocated. Thus, the subject has again become a matter of controversy, which can be settled only by impartial appraisal and analysis of the 5 year survival rates in comparable series of patients treated by each of the available methods. To this end, additional data will be essential, for present evidence does not yet permit any final conclusions about the optimal form of treatment in cancer of the cervix. These considerations prompted the present report, dealing with survival rates, complications, and possible causes of failure in a series of patients treated at the New Haven Hospital, a general hospital of 510 beds, during the years 1934 to 1941, inclusive.

CLASSIFICATION OF PATIENTS

One hundred fourteen patients with cervical cancer were treated during this period. Of these, 88 were ward patients who received primary radiation therapy. In addition, there were 12 private patients, 9 others whose primary treatment was given elsewhere and who were admitted with advanced or terminal disease, and 4 patients in whom the diagnosis of carcinoma of the cervix was not clearly established by biopsy. In 1 patient, a very early lesion was first discovered in the surgical specimen after total hysterectomy. These miscellaneous groups have been omitted from further study and our attention has been centered on the 88 ward patients because a relatively homogeneous and uniform treatment plan and clinical work-up program was adhered to in this group, and because their follow-up data are most complete.

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The ages of the 88 patients in this selected group ranged from 25 to 81 years, with the greatest concentration of cases in the two decades, 40 to 49 years and 50 to 59 years. The distribution by decades, and the number of 5 year survivals per decade, are presented in Table I. It can be seen that the age of the patient, *per se*, was not of great prognostic significance. With the exception of patients in the youngest decade, these results are in accord with those reported for a larger series by Healy and Frazell. This finding is at variance with the widespread notion that the outlook for very young patients with cervical cancer is particularly unfavorable. Such patients merit just as prompt, aggressive, and thorough treatment as women over 50 years of age.

TABLE I.—AGE AND SURVIVAL DISTRIBUTION BY DECADES

Age, years	20–29	30–39	40–49	50–59	60–69	70–79	80 and over
No. patients	3	16	23	25	15	5	1
5 year survivors	2	6	8	9	5	2	1
Survival per cent	66	37	35	36	33	40	..

Bleeding of variable severity was by far the most common presenting symptom. Aching pain in the lower back or pelvis and foul vaginal discharge were also frequent complaints, while weight loss of significant degree was seldom observed initially. Four patients had no symptoms referable to their tumors; these were detected only during routine physical examinations for unrelated complaints. The duration of symptoms prior to diagnosis varied from a few days to a few years, but this factor appeared to have little or no relation to prognosis or to the extent of disease on initial examination. The fact that the survival rate in

patients with symptoms for over 2 years was just as high as that in patients in whom the diagnosis was made "earlier" is probably best explained by variations in the growth rates of the tumors and in the ease with which they bled.

CLINICAL EVALUATION AND METHOD OF TREATMENT

The patients are usually referred from the admitting clinics or from other services where they have been seen. Although the hospital maintains a general tumor clinic, staffed by radiologists, pathologists, and surgeons, it has been found more convenient to send these individuals to a special tumor clinic operated by the Department of Obstetrics and Gynecology, in which patients with neoplasms of the female genital tract are examined, prepared for treatment, and subsequently followed. In addition, a central tumor registry, supported by grants from the Jane Coffin Childs' Fund for Medical Research, maintains a crossfile index of all tumor cases and is charged with the responsibility of getting patients back regularly for periodic follow-up examinations.

Patients with suspected cervical cancer are examined bimanually in the special clinic and, if this examination is confirmatory, are admitted to the hospital as emergency cases. There, a detailed history is taken and a complete physical examination and biopsy of the cervix are performed. When the biopsy is reported positive for carcinoma, the patient is subjected routinely to all of the following diagnostic procedures: (1) cystoscopy, (2) intravenous urography (retrograde also when necessary), (3) sigmoidoscopy, and (4) roentgen examination for metastases, which includes a posteroanterior chest film, anteroposterior and lateral films of the abdomen, pelvis, and lumbosacral spine, and a single lateral view of the skull. When all of this information concerning the patient is available, she is seen jointly by the tumor therapy representatives of the Departments of Obstetrics and Gynecology and of Radiology, who perform a careful abdominorectovaginal examination to map out the extent of palpable disease, and then reach a decision concerning the optimum method of treatment in each particular case. Cases have been classified according to the League of Nations plan.

Although an attempt is made to individualize treatment, attention is also directed to the dangers of excessive empirical variation in technique, and a relatively routinized method has been employed wherever possible in order to facilitate subsequent evaluation of results.

In the usual case, treatment starts with external roentgen therapy. It is generally agreed that roentgen radiation should precede rather than follow radium application because it reduces infection in the primary tumor, causes its regression, thus facilitating subsequent radium insertion, and tends to seal off the parametrial lymphatics, slowing the spread of disease. Following the recommendations of Arneson and Quimby (2), which were based on a study of the physical distribution of external roentgen radiation in the pelvis, 6 portals (2 anterior, 2 posterior, and 2 lateral) have been employed on all patients whose anteroposterior abdominal measurement was 20 centimeters or more. The lateral portals have been omitted on thinner patients. The usual portal size has been 10 by 15 centimeters, with the inferior outer corner shielded off by lead on the anterior and posterior fields to protect the femoral head. The physical factors have been: 200 kilovolts pressure, 20 milliamperes, 70 centimeters distance, ½ millimeter of copper plus 1 millimeter of aluminum added filtration, output 22 roentgens per minute. After the first pelvic cycle of 6 daily treatments, 2 portals are treated daily, each receiving approximately 250 roentgens. Thus, in a 3 to 4 week period a total dose of 1500 to 1800 roentgens, measured in air, is delivered to each of the 4 to 6 portals

The patient is seen in the gynecological tumor clinic 2 to 4 weeks after the completion of x-ray therapy, re-examined, and scheduled for hospital admission and radium insertion. Ordinarily, repeat biopsies are not done during or after treatment, as it is felt that they may interfere with the healing process and possibly break down fibrous barriers around damaged but still viable cancer tissue.

Radium insertion has been performed under general anesthesia about 4 to 6 weeks after the course of roentgen therapy is finished. This

time interval was selected to permit maximal regression of the tumor and subsidence of the radiation reaction, with the feeling that radium application would thus be facilitated and late injuries minimized. The question of the optimal interval between external therapy and radium insertion will be treated at greater length in the discussion below.

For the treatment of cervical cancer, platinum cells having a total length of 12 millimeters, an active length of 11 millimeters, and a wall thickness of 0.2 millimeter, and each containing 3.33 milligrams of radium, are enclosed in platinum tubes having a wall thickness of 0.3 millimeter, an active length of 12 millimeters, and an overall length of 15 millimeters. Each platinum tube holds either 4 or 8 cells. These tubes are then placed individually in hollow brass cylinders 7 millimeters in diameter, about 20 millimeters in overall length, each having a wall thickness of 2 millimeters (0.5 mm. pt. equivalent). Thus the total metallic filtration is equivalent to 1.0 millimeter of platinum.

For intrauterine application, 2 or 3 cylinders are inserted in tandem into a short length of black rubber tubing which is then tied off at both ends. Eight radium cells are usually placed in the inferior cylinder, which lies close to the lower end of the uterine canal, and only 4 cells in the upper cylinders. Cylinders, containing 4 cells each, are also placed in the hollow rubber corks of a conventional colpostat, and, where possible, in a third rubber cork which is placed inside the circle of the colpostat bridge against the external os of the cervix. This is essentially the "Paris technique" developed by Regaud and others. After insertion of the radium, the vagina is carefully packed with sulfathiazole-impregnated gauze packing, care being taken to displace the bladder and rectum as far from the radium sources as possible. An indwelling catheter is left in the bladder.

In those cases in which the extent of the tumor does not interfere with the standard radium application described, a total dosage of 6,000 milligram hours has been employed, divided equally between the tandem and colpostat. In the years 1934 to 1936, it was customary to insert the tandem first, followed after an interval of 4 or 5 days by the introduction of the colpostat. More recently both applicators have been used simultaneously; the total duration of radium exposure is approximately 70 hours.

Seventeen of the 88 patients received no radium therapy because, due either to the local extent of disease or to systemic complications, it was felt that radium therapy would not add to the palliation effected by external roentgen treatment alone. Conversely, 6 early lesions in which the disease was apparently confined to the cervix were treated by radium alone. In a small number of cases in which combined roentgen and radium therapy was planned, either one or the other was not completed, owing to the development of complications, to failure of the patient to return for treatment, or to errors in follow-up. Thus a net total of 58 patients received a full course of radium treatment and 52 of these also received roentgen therapy in the usual dosage range.

RESULTS

The results of radiation therapy in the series of 88 primary ward cases are summarized in Table II. The 5 year survival rates, expressed as percentages of the determinate group, are: 69 per cent for Stage I, 47 per cent for Stage II, 4 per cent in Stage III, and 0.0 per cent in Stage IV. The net 5 year survival rate for the entire series was 38 per cent.

In 3 instances, patients who had survived 5 years developed recurrences and died of cancer after 6, 7, and 10 years, respectively. One other patient is living with extensive recurrent disease 7 years after treatment. It is generally accepted that about 10 per cent of those with cervical cancer who survive 5 years will subsequently die of the disease. About half of the patients in our group of survivors have now been followed for 8 to 13 years.

Complications. The number of recorded complications in this series was surprisingly small, and they appear to be complications of the disease process itself rather than the result of treatment. Two patients had a second primary cancer; one arose in the ovary, the other in the breast. These were both far advanced when the cervical cancer was detected and only palliative treatment could be given.

TABLE II.—RESULTS OF RADIATION THERAPY IN 88 CASES OF CERVICAL CANCER

	Stage I		Stage II		Stage III		Stage IV		Total	
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Total primary ward patients	37	100	17	100	25	100	9	100	88	100
Lost to follow-up	1	2.7	0	0	0	0	0	0	1	1
Dead of other causes	1	2.7	0	0	0	0	0	0	1	1
Determinate group	35	95.	17	100	25	100	9	100	86	98
Dead of cancer less than 5 years	11	31.*	9	53*	24	96*	9	100*	53	62*
Dead of cancer more than 5 years	3								3	
Alive—5 years	24	69.*	8	47*	1[b]	4*	0	0.0*	33	38*

*Percentages of the determinate group.

One patient who survived 5 years subsequently developed a basal cell carcinoma of the skin of the face which was recently treated.

The presence of vaginal fistulas communicating with either the rectum or bladder at the time of death was recorded in 3 patients. All of these fistulas developed long after radiation therapy, in areas of extensive neoplastic involvement, and it seems reasonable to conclude that they resulted from the disease rather than from radionecrosis. There were no instances of fistulas or intestinal stricture, obstruction, or perforation which could be attributed to the radiation therapy employed. These results contrast favorably with the incidence of radiation injuries and fistulas reported elsewhere. Smith found a higher incidence of fistulas in untreated patients than in patients treated with radium and roentgen rays in fractionated or massive doses, and concluded that most fistulas can be considered part of the natural course of the disease. That certain methods of treatment are attended by a significantly greater hazard of fistula formation is indicated by the reports of Pitts and Waterman (15), who observed 29 fistulas in 373 patients treated by interstitial radium implantation, with or without supplementary roentgen therapy. Recently Meigs (8) advocated a return to the Wertheim operation in the treatment of early cancers of the cervix. Although the mortality in his series of 53 patients was only 1.9 per cent, he noted 5 ureterovaginal fistulas, an incidence of 10.6 per cent. Corscaden, Kasabach, and Lenz found that the incidence of intestinal radiation injuries could be brought down from 8.7 per cent to zero by increasing the time and reducing the intensity of treatment. It seems reasonable to conclude that fistulas and other complications may occur as the result of the technique and dosage employed but are not an inevitable sequel to all radiation therapy for cervical cancer.

Metastases. Despite the contrary evidence provided by a number of studies in advanced cervical cancer, the clinical impression still persists that remote metastases from carcinoma of the cervix are uncommon. Behney noted distant metastasis in 44 per cent of a series of untreated patients and in 21 per cent of treated patients coming to autopsy. Pearson has reviewed the earlier literature on this subject and added his findings in 57 cases of cervical cancer examined postmortem. In this group there were 13 (25 per cent) with remote metastases to the liver, lungs, pleura, peritoneum, kidney, bones, or spleen.

In the series reported here, 56 patients died of cancer, and 13 of these (23.2 per cent) are known to have had distant metastases at autopsy. The actual incidence is undoubtedly higher, inasmuch as many patients died at home where postmortem examination was not possible. At the time of treatment, 5 of these 13 cases had been classified as Stage I, 1 as Stage II, 4 as Stage III, and 3 as Stage IV, but all were clinically very extensive by the time death occurred or metastases were noted. Thus, remote metastasis is a rather frequent event in carcinoma of the cervix, particularly in relatively advanced cases.

TABLE III.—COMPARISON OF PUBLISHED RESULTS IN RADIATION-TREATED CASES OF CERVICAL CANCER

Author	Treatment years	Total number of cases	Classification	Per cent "operable"	Net 5 year survival rates, per cent					Remarks
					Stage I	Stage II	Stage III	Stage IV	Total	
Pitts and Waterman	1926–1930	173	S.	36	90	54	29	0	31.8	Radium alone
Waterman and DiLeone	1936–1938	109	S.	..	100	69	29	4	44.9	Radium and x-ray
Holt Radium Institute	1934–1938	826	L.N.	41	65	42	27	6	28	
Hurdon (Marie Curie Hospital)	1930	136	L.N.	28	83	66	33	18	41	
Lacassagne (Institut du Radium)	1930	111	L.N.	45	75	56	34	36	47	
Meigs and Jaffe	1933	70	A.C.S.	11	100	67	35	6	34	
Healy and Frazell	1928–1931	551	L.N.	30	58	38	22	6	28	
Authors	1934–1941	88	L.N.	61	69	47	4	0	38	

S., Schmidt classification.
L.N., League of Nations classification.
A.C.S., American College of Surgeons classification, similar to League of Nations.

DISCUSSION

Accurate evaluation of the effectiveness of any particular treatment method in cancer of the cervix must depend upon the availability of truly comparable control data. Ideally, it is desirable to study the results of two or more treatment methods as applied concurrently to patients entering a single clinic where they are divided at random into the proper number of groups of similar clinical extent. That there are significant differences in the skill and accuracy with which cervical cancers are classified as to stage by different observers in different clinics cannot be doubted. This important source of error is largely eliminated when parallel groups are examined and treated by the same group of physicians in a single clinic, and recent studies of this type (22) may, accordingly, be regarded with greater confidence. Unfortunately, it has not been possible, in most institutions, to gather data in this manner, and end-results achieved by a particular technique in one clinic can be compared only with published reports from other sources. Even when care is taken in the selection of these comparative reports to eliminate those which are outdated or based upon an obviously different scheme of classification, an error of undetermined magnitude must still be anticipated. With these considerations in mind, we may attempt to assess the flaws and strengths of our treatment method.

When the net 5 year survival rates are compared by stages, as in Table III, it can be seen that our results for the "operable" Stages I and II are in fairly good agreement with those achieved elsewhere. Since roughly similar results have been achieved by the use of radium alone in these stages, and particularly in Stage I, it would seem reasonable to conclude that external roentgen therapy adds little or nothing in these cases and may well be omitted.

However, when the results in Stages III and IV are studied, they are seen to fall far below those reported by a number of other institutions in recent years. Even if one were to grant that part of this discrepancy is due to differences and errors in clinical classification it must still be admitted that most cases so classified, both here and elsewhere, properly belong in the stages mentioned. Since we cannot fully explain away these poor results on some other basis, they must be charged to deficiencies in our treatment plan, and it becomes necessary to search for the weak points. This requires a step-by-step review of our method of treatment.

It is clear that the entire responsibility for these poor results in advanced cases cannot be thrown upon the method of treatment *per se*. Errors in technique or dosage, occasional negligence in follow-up, and the deliberate omission of radium therapy in those patients in whom palliative treatment was deemed advis-

able have interfered with the administration of a full course of treatment in many cases. A review of these instances reveals that 3 patients failed to return for radium therapy at the appointed time and, through an oversight, were not sent for through social service channels. These cases were classified as Stage I, II, and III, respectively, and all 3 failed to survive 5 years. In 4 other Stage I cases, an interval of 2 to 12 months was allowed to elapse between roentgen and radium therapy for similar reasons, but radium was ultimately applied and 3 of these patients are still alive.

Ten patients received incomplete radium therapy as a result of the omission of either the tandem or colpostat. In most instances, this was due to difficulty encountered in the insertion of the applicators into a stenotic external os or vaginal vault, or to the presence of a "stump" carcinoma with a short uterine canal. The net result was an inadequate total dose and unsatisfactory distribution of the radiation, which should have been corrected in part by an increase in dosage from the other applicators, and their reinsertion if necessary after a short interval. These 10 cases were classified in Stages I to III, and none of these patients survived 5 years.

Finally, a group of 17 patients (9 Stage IV, 6 Stage III, 2 Stage II) received no radium treatment because they were regarded as too far advanced or too old for anything but palliative external radiation. One of the patients with a Stage II lesion was 81 years old at the time of treatment and is still alive and well 11 years later; none of the other 16 patients survived 5 years. In the other patient with a Stage II lesion the coexistence of an extensive inoperable ovarian carcinoma was the reason for withholding radium. While it cannot be doubted that overenthusiastic treatment of patients with Stage IV cancers of the cervix often does more harm than good, it is also true that better palliation can be achieved in some instances by the use of radium as well as external roentgen therapy, and the omission of radium in Stage III cases deprives about 1 patient in 4 of a chance for a 5 year survival. Obviously extreme debility or constitutional infirmities may contraindicate the insertion of radium even in patients in whom the local extent of disease is not great. This situation did not obtain in the majority of patients from whom radium was withheld. In view of our poor results in Stage III and IV cases, the decision to omit radium therapy in almost one-half of such patients appears to have been unduly conservative.

We may now consider the possible flaws in our basic plan of using external roentgen therapy followed, after an interval of 4 to 6 weeks, by the insertion of radium according to the Paris technique. Sandler (16) has clearly indicated the extent to which the width of the upper vagina may influence the radium dosage delivered to various points in the lateral parts of the true pelvis. It is a common observation that stenosis of the upper vagina may follow external roentgen therapy, and, in a few instances in this series, subsequent radium treatment had to be modified or abandoned because of this complication. This stenosis appears to progress rapidly within a few weeks after radiation, and a relatively long interval between roentgen and radium therapy therefore tends to increase the frequency with which the condition is encountered when radium insertion is attempted. Secondly, after the relatively long interval of 6 weeks almost all of the tissue reaction to preliminary roentgen therapy has disappeared, and a given dose of radium at this time will be relatively less effective than the same dose administered 1 or 2 weeks after the course of roentgen radiation. Thus a relatively long interval has the two-fold effect of decreasing the biological response to a given dose of radium at the same time that it increases the difficulty of applying such a dose.

On the other hand, it is to be expected that a shorter interval between x-ray and radium treatment will be attended by a greater incidence of radiation injuries, as the work of Corscaden, Kasabach, and Lenz has indicated. A delicate balance must therefore be struck and an interval selected which will afford maximal effectiveness coupled with reasonable safety. In our series the number of complications which could properly be charged to radiation injury was extremely small, but this alone does not compensate for the poor survival rates in the relatively advanced cases. Sandler (17) and Tod (23) at the Holt Radium Institute,

Manchester, have advocated the use of radium either before and after roentgen therapy, or its insertion within 1 to 2 weeks thereafter, in order to avoid the curtailment of lateral dosage which even moderate vaginal stenosis brings about.

The question of optimum radium and roentgen dosage cannot yet be answered for lack of adequate data. In a large series of patients treated at the Holt Radium Institute, Tod (23) found that the greatest survival rates occurred in patients treated with intermediate dosage, and that necrosis following very high dosage was often associated with residual or recurrent cancer and an increased number of fatalities, which she referred to as the "supralethal effect." On this basis, it is desirable to use the highest dosage compatible with safety; this can be established only by empirical trial with each technique. Our radium dosage has been 6,000 milligram hours, divided equally between the tandem and colpostat, and this appears to have been both adequate and safe in the early cases. It is probable, however, that an increase in dosage to 7,000 or even 8,000 milligram hours in Stages II and III would bring some improvement in survival rates without unduly increasing the number of complications. A similar increase in external roentgen dosage would probably be of negligible value since it is generally agreed that roentgen therapy plays a minor rôle in the treatment of cervical cancer.

We may next turn to a consideration of the radium treatment method which may be expected to provide the best results. For many years, the two major techniques in vogue were, with minor modifications, the "Paris technique" of Regaud described above, and the "Stockholm technique" of Heyman, in which a tandem applicator is inserted into the uterine canal and variously shaped flat metal boxes are placed against the external surface of the cervix and, when possible, obliquely in the fornices. These methods have been seriously challenged within the past 10 years, and at least two other radium techniques have been recommended in their place.

The use of interstitial radium needles in conjunction with an intrauterine tandem was first advocated by Pitts and Waterman (15) and has gained increasing support recently (1, 25). As modified by Nolan and Quimby it permits the administration of relatively larger doses of radiation to the lateral zones of the parametria. The clinical results reported by Pitts and Waterman and by Waterman and DiLeone (25) seem to compare favorably with those attained elsewhere, particularly in relatively advanced cases, but accurate comparison is impeded by their use of the Schmidt rather than the League of Nations scheme of classification. Many therapists have objected to the method on the ground that it is an essentially "blind" procedure as a result of which the radium needles might enter the peritoneum, puncture the intestine, or lie dangerously close to the ureter or large pelvic arteries. Even in the hands of its innovators the method was attended by a mortality of 2.9 per cent and produced 29 fistulas in 373 cases. It seems reasonable to anticipate an even greater incidence of complications when this technique is used more extensively by others. Recently, Taylor and Twombly (22) published a preliminary report on the effectiveness of this method as compared with the use of intravaginal roentgen therapy in the treatment of two parallel and clinically similar series of patients with cervical cancer. Although a 5 year period has not elapsed, the survival rates to date are distinctly unfavorable to the needle technique, and the frequency of severe bladder and rectal symptoms and of local necrosis has been considerably higher in the group thus treated. This method undoubtedly deserves further study but available evidence does not support claims for its superiority and would indicate that it is unsuitable as a routine procedure.

The group working at the Holt Radium Institute in Manchester has evolved hard rubber "ovoids" for the application of radium to the vaginal vault. These are used in conjunction with an intrauterine tandem in what is essentially a modification of the Paris technique. The applicators and the method of dosage estimation have been well described by Tod and Meredith (24). Physical studies have clearly shown that a more homogeneous and laterally more effective distribution of radiation can be achieved than with the older Stockholm and Paris techniques and the estimation of gamma

roentgen dosage to various points in the pelvis is facilitated with these standard applicators. For these reasons a thorough trial of the Manchester technique by American clinics would seem indicated.

Several years ago Merritt advocated the substitution of intravaginal roentgen therapy for radium in the treatment of cervical cancer. Because of difficulty in directing the beam laterally, especially in patients with a narrow vaginal vault, the distribution of radiation in the pelvis was found to be inferior to that obtained with standard radium techniques (11). Recently, however, a combined method has been tried at the Memorial Hospital, New York, in which the intrauterine radium tandem is still employed and only the vaginal applicators (colpostats, bombs, boxes) are replaced by intravaginal roentgen therapy. Initial reports on this modification, as cited above, seem quite favorable (22).

In 1945 Meigs (8) boldly challenged the accepted radiotherapeutic techniques and suggested a return to the radical panhysterectomy of Wertheim. At the time of his report, he had performed this operation in 47 elective cases with no deaths and in 6 nonelective cases with 1 death. This low mortality sharply emphasized the advances made by surgery through the introduction of improved operative techniques, more scientific preoperative and postoperative care, and the advent of chemotherapy. For years the chief argument against the Wertheim procedure was the high mortality with which it was attended, even in the best hands. It is clear that the situation has changed and that the place of surgery in the treatment of cervical carcinoma is in need of re-evaluation. It is not likely, however, that this method will supplant radiation therapy to any large extent because such low mortality rates can be achieved only by highly experienced surgeons who carefully select their cases. Meigs required his elective cases to be "thin, young, in good health" and to have an early tumor. The majority of his patients apparently had early Stage I lesions, which are also most susceptible to radiation therapy. One of the prime reasons cited by Meigs for his return to surgery is the frequency with which the pelvic lymph nodes are involved by occult cancer which, he believes, cannot be eradicated by radiotherapy. In his series of 53 patients, examination of the lymph nodes in the operative specimen revealed cancer in 8 (17 per cent) but the clinical stage of disease in these cases is not stated. Obviously no final evaluation of the revived Wertheim operation can be made until 5 year survival rates are available for a large series of cases carefully classified by stages. On *a priori* consideration, however, it appears that prohibitive mortality rates will limit its use to early cases, in which lymph nodes are less often involved and for which suitable radium therapy already offers a very good prognosis.

For many years Taussig (19, 20) advocated iliac lymphadenectomy as a supplementary measure in the treatment of carcinoma of the cervix. Recent improvements in the operative technique have made this a rather simple, safe extraperitoneal procedure which permits the eradication of pelvic lymph nodes almost as effectively as the much more extensive Wertheim operation. The claim by many surgeons that present methods of radiation therapy cannot eradicate cancer in the pelvic lymph nodes is not without foundation. It is generally agreed that metastatic cancer in the submaxillary and cervical nodes cannot be completely destroyed by external radiation alone, and that such deposits are best treated by radical neck dissection. The situation in the pelvis is highly analogous to that in the neck, particularly since most of the tumors are epidermoid carcinomas similar to those arising in the mouth. On this basis alone it would seem illogical to expect external radiation (which includes surface radium therapy as well) to accomplish in the pelvic nodes what it cannot do in the neck.

Further support for this point of view is furnished by a comparison of the survival rates and the frequency of lymph node involvement in cancer of the cervix. In Stage I cases, 5 year survival rates have ranged between 60 and 100 per cent, with a rough average for the larger series at about 70 per cent. In Stage II, a similar estimate would be about 45 per cent, and in Stage III, about 25 per cent. Taylor (21) has reviewed the literature pertaining to the frequency of pelvic lymph node involve-

ment. He found that regional metastases had occurred in about one-third of "operable" cases, and that the incidence of involvement jumped from about 15 per cent in patients in whom the parametria were microscopically free of cancer to 35 to 55 per cent when one or both parametria were directly invaded. If allowance is made for patients dying because of failure to control the primary lesion, it is clear that most of the deaths from cervical cancer *could* be accounted for on the basis of uncontrolled lymph node involvement.

It seems probable, therefore, that combined roentgen and radium therapy as employed today is incapable of eradicating cancer in the pelvic lymph nodes. More widespread recognition of this fact will undoubtedly result in a renewed trend toward surgery. It would seem that in Stages I, II, and III, a combination of radium and roentgen therapy directed at the primary lesion and its direct lateral extensions, followed by extraperitoneal lymphadenectomy to clean out possible regional metastases, would be a conservative and probably effective step in the right direction.

SUMMARY AND CONCLUSIONS

1. The results in a series of 88 patients with carcinoma of the cervix treated by combined roentgen and radium therapy in a general hospital have been reviewed. The net 5 year survival rate for the whole group was 38 per cent, which compares favorably with that reported elsewhere. However, when analyzed by stages, almost all of the 5 year survivals were noted to have occurred in the disproportionately large group of "operable" Stage I and II cases, and the results in more advanced cases are thus shown to have been unsatisfactory.

2. Possible technical modifications which might yield better results are discussed, and it is concluded that the interval between roentgen and radium therapy should be shortened from 6 weeks to 2 weeks or less, that radium dosage should be increased somewhat in advanced cases, that the "Manchester technique" of radium application should be adopted, and that extraperitoneal iliac lymphadenectomy should be performed after irradiation in Stages I, II, and III to save patients with regional lymph node involvement.

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EXPERIMENTAL STUDY ON LIPOCAIC

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As a result of experimental studies on fatty infiltration of the liver caused by the removal of the pancreas in dogs, Dragstedt and associates (8, 11) reported having obtained a fat-free alcoholic extract from fresh beef pancreas, with which they claimed to have prevented fatty degeneration of the liver and death of depancreatized dogs that had received insulin and were fed on bread, milk, and meat.

As choline was not the specific principle of this extract, nor was it to be found in the pancreatic juice or in the extracts of other organs with a rich lipoid content (brain, liver) and in view of the fact that it was found to be active in small doses per os, Dragstedt considered it to be a pancreatic hormone different from insulin and indispensable to the normal metabolism of lipids; moreover, he suggested the name "lipocaic" for it (11). According to Dragstedt, daily doses of 1 to 1.5 grams of the original preparation (equivalent to 100 grams of fresh pancreas) given by mouth, prevented or cured a gross lipoid surcharge of the liver and other typical symptoms present in depancreatized dogs treated with insulin.

Dragstedt's hormonal theory, based on experimental evidence not entirely unassailable, was subjected to numerous criticisms. Some of these were successfully answered by him and his co-workers (9, 12) but other questions are still open to discussion, partly owing to a lack of uniformity among authors not only concerning the methods used for giving rise to fatty infiltration of the liver but also regarding the diets given to animals.

Though the hormonal character of lipocaic is still denied by some, experiments carried out on various types of laboratory animals—particularly on dogs and rats—prove that Dragstedt's extract has an unquestionable lipotropic activity which is not due to the presence of insulin, lecithin, choline, proteins (6, 7, 31), methionine (7), or inositol (25, 30).

Our work was undertaken with the purpose of studying experimentally (a) the metabolic changes occurring in dogs with ligated pancreatic ducts, (b) the repercussions which this operation has on the chemical composition of blood, and (c) the preventive and healing effects that the lipotropic principle of the pancreatic extract—prepared after Dragstedt's technique—has on both (a) and (b). Following other authors' footsteps, we started by studying the variations of the cholesterol and phospholipid content of the blood of those animals, with the object of endeavoring to establish a quantitative relationship between these and the dose of extract administered.

The first observations suggested that the ligation in dogs of the excretory ducts of the pancreas because of the fatty infiltration of the liver it caused (1, 2, 16, 24, 26, 28, 29) necessarily had to produce some changes in the functional activity of this organ. Therefore, we carried out further researches on both the prothrombin variations and the blood's alkaline phosphatase activity. In some cases we also determined the serum proteins in order to investigate the effect of their decrease on the alterations already observed.

METHODS

The experiments were performed on 10 normal dogs of different sizes, in which the pancreatic ducts were ligated according to the technique advocated by Montgomery, Entenman and Chaikoff. A 10 centimeter long midline incision was made, the cut being carried right down to the peritoneum. Once the entire duodenum and pancreas had been delivered and the duct of Wirsung and accessory ducts came into view, they were cut between two cotton ligatures. All pancreatic attachments to the duodenum were severed; the dissection was carried down to a distance of 2

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centimeters beyond the lower duct. Only the larger blood vessels were left untouched. Finally pieces of omentum were placed between the pancreas and duodenum and were secured in position by cotton sutures. The abdominal wall was closed in 2 layers, cotton being used in both. Interrupted stitches were used for the fascia and subcuticular sutures for skin.

The dogs were given no food for 48 hours after operation. After this time, feeding was started with meat, bread, milk, and sugar. Plenty of water was allowed. This basic ration was used in all experiments. The pancreatic extract for testing was given to the animals in gelatin capsules which were later mixed in the meat. In some cases biopsies of liver tissue were made during the course of the experiment. Necropsy was performed in all animals in order to ascertain the degree of pancreatic atrophy and to remove samples of different organs for pathological study. These specimens were fixed in formalin and embedded in paraffin. The histological sections were colored with hematoxylin-eosin.

Chemical determinations in blood. For the purpose of studying the effect of the ligation of the pancreatic ducts on some of the blood components and the action of lipocaic on them, the following periodical determinations were carried out: blood sugar (Folin's method), cholesterol in serum (Schoenheimer and Sperry's method), phospholipid in serum (total phospholipids: Subbarow and Fiske's method adapted by Marenzi to a photometer), prothrombin concentration in plasma (Tanturi and Banfi's technique), serum proteins (by pyknometry, after Moore and Van Slyke's indications), and alkaline phosphatase in serum (Shinowara, Jones and Reinhart's method). In the latter a modification in the assay of phosphates was introduced and Holman's method was used. In all animals blood was extracted during fasting. Every determination was done within 12 hours of obtaining the samples, and only those samples of serum and plasma wholly exempt from hemolysis were used.

PREPARATION OF PANCREATIC EXTRACT WITH LIPOTROPIC ACTIVITY (LIPOCAIC)

Dragstedt's technique, with certain modifications, was employed for preparing the pancreatic extract (11).

Fresh pancreas from cattle were passed through a mincing machine and the mass was then left to macerate for 24 hours in twice its volume of 96 per cent alcohol, the mixture being shaken at intervals. Once the hydroalcoholic layer had been decanted, the residue was subjected to further extraction with 60 per cent alcohol for a second 24 hours. At the end of this period, the extractive fluid was mixed with the former—which had been kept in cold storage—and the residue was macerated twice again. It was proved later that the fourth extraction was useless, so this fourth step has been discontinued.

Finally the residue was squeezed through gauze and all the extractive fluids were mixed and distilled at vacuum at a low temperature (maximum external: 43° C.; internal: 35° C.) in order to recover the alcohol, which could be used again in the second and third extractions.

As the alcoholic content of the extractive fluid decreases during the distillation process, the lipids are freed and appear on the surface in the shape of flocculi. These are easily removed by filtration. Thus Dragstedt's costly method of fat-extraction by means of ether is dispensed with. After we devised this method Dragstedt (7) modified his technique, eliminating ether process of fat-extraction.

The watery fluid resulting from distillation contains the lipotropic principle. This fluid was filtered and concentrated by vacuum over sulfuric acid and at room temperature, until a thickish substance was obtained. This substance was made into a homogeneous paste by adding 30 per cent of its weight of powdered sugar for preservation purposes, and mixing with a spatula. Later gelatin capsules were filled with this paste (approximately 0.75 gram per capsule) and were immediately placed in wide-mouthed glass containers with frosted glass stoppers. These containers were kept in an icebox to prevent the capsules from coming into contact with a humid atmosphere.

The product described is the one we used per os in our experiments. When testing its activity by the systemic route, we used the powder obtained by drying the pure extract; no sugar was added and the powder was aseptically dissolved in sterile saline.

We were able to prove the absence of lipids in our preparation by extracting with ether, in a Soxhlet apparatus, the powder obtained by total drying of the sugarless extract; the residue thus found, is practically negligible. It was this powder, thus extracted with ether, which we used in some physical and chemical determinations.

Yield. The yield can be calculated in terms of dry extract, fluid extract, or extract with sugar.

Five kilograms of fresh pancreas gives an average of 200 grams of fluid extract, that is, the equivalent to a 4 per cent yield.

As the fluid extract contains 30 per cent of water the 5 kilograms of fresh pancreas are equivalent to 140 grams of dry powder (Dragstedt's lipocaic), which means that the yield in dry powder is of 2.8 per cent.

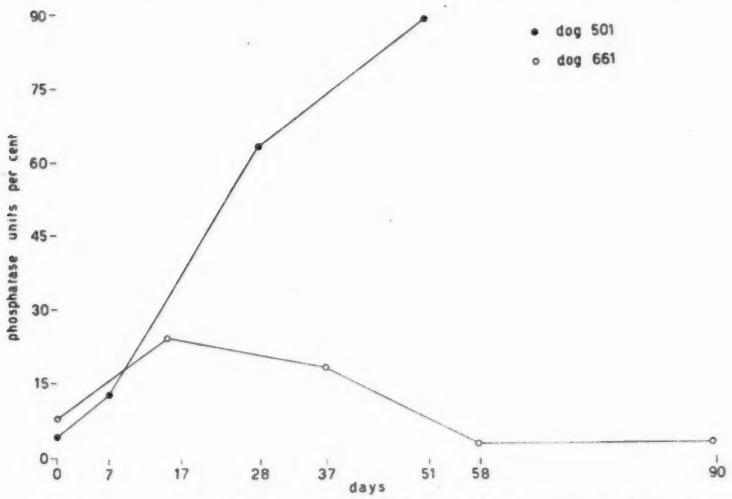

Chart 1. Increase in the alkaline phosphatase of serum of the untreated animals (such as in dog 501). Note the difference between the animal treated with lipocaic (dog 661).

For calculating the yield in terms of extract with sugar, it must be taken into account that 60 grams (30 %) of sugar are added to the 200 grams of fluid extract; thus, the yield will be 5.2 per cent.

Bearing in mind these results, the following relation may be established: 1 gram of extract with sugar =0.77 gram of fluid extract =0.538 gram of dry extract (Dragstedt's lipocaic); therefore, one of our capsules containing an average of 0.75 gram of extract with sugar, is equivalent to 0.4 gram of dry extract or to 14.3 gram of fresh pancreas.

Characteristics of the extract. The sugarless extract is a thickish substance, of a very light brown color, with a strongly salty taste reminiscent of certain cheeses, and has a special smell. When completely dry, it is a golden colored powder, very hygroscopic, insoluble in ether, but easily dissolved in water, as well as in hydroalcoholic solutions, diluted acids and saline.

The aqueous solution of the dry extract has no reducing action on Benedict's reagent and its alcohol-ketonic extract does not precipitate with digitonin, either directly or after saponification with potassium hydroxide. There was no demonstrable tryptic activity with Gross's method.

Ashes. By the usual method of calcination, the average sample gave *17.2 grams of ashes for every 100 grams of dry extract.*

Total nitrogen. In two average samples, the total nitrogen was assayed by Kjeldahl's method. By distillation with Goldberg and Banfi's apparatus (18), the resulting ammonia was collected in a measured volume of sulfuric acid of known normality, and then valued by photocolorimetry with Nessler's reagent.

Results. Sample 1: 11.6 grams of total nitrogen for every 100 grams of dry extract. Sample 2: 10.02 grams of total nitrogen for every 100 grams of dry extract.

Average: 10.31 grams of total nitrogen for every 100 grams of dry extract.

These figures agree with those given by Dragstedt when using his own extract (7). According to him, lipocaic prepared by means of his modified technique contains 1.25 grams of methonine and no choline (7).

TESTING THE PANCREATIC EXTRACT

The lipotropic action of the pancreatic extract was tested both as a preventive and corrective agent. This was done by administering it either immediately after ligating the pancreatic ducts (dogs 621, 661, and 681) or at intervals ranging between 58 and 161 days after the operation (dogs 503, 524, 526, 544).

The extract was given by the oral route (capsules) or systemically (subcutaneous injection of the extract dissolved in distilled water or sterile saline solutions).

The different preparations used in our experiments were:

Lipocaic: pancreatic extract prepared by us according to our modification of Dragstedt's method. One capsule contains the equivalent of 14.3 grams of fresh pancreas. For systemic administration, an equivalent amount of dry extract was dissolved in 3 milliliters of distilled water or sterile saline.

Y preparation: a pancreatic extract, prepared as above at a laboratory of medicinal products. We are not familiar with its precise equivalent in terms of fresh pancreas, though we believe it is very close to that of our preparation.

X preparation: an aqueous solution of a pancreatic extract, for intramuscular injection, manufactured by a firm of medicinal products. According to the makers, each ampul contains 200 milligrams of active substance (2 ml.) and 0.3 per cent of phenol. Its equivalent in terms of fresh pancreas is unknown.

Z preparation: pancreatic autolysate in aqueous solution, for intramuscular injection. Also a commercial preparation. Its nitrogen content is not known.

Casein hydrolysate: Prepared after the method of White and Elman (37) by boiling during 6 hours in 2.6 normal sulfuric acid and then precipitating the acid surplus with barium hydroxide. The solution of amino acids, to which 5 per cent glucose was added, was divided and put in sterilized tubes and rendered aseptic by tyndallization. According to Kjeldahl's method, 20 milliliters of this solution contain 267 milligrams of total nitrogen. The slow intravenous injection of this preparation caused no intolerance or anaphylaxis in dogs.

RESULTS AND COMMENTS[1]

No trouble was ever experienced in feeding or administering the lipocaic capsules in the postoperative stage, as the animals always had good appetites. However, all of the dogs lost weight during the experimental period. Their stools were of normal appearance at first, but after 2 to 3 weeks they became bulky, thickish, of grayish color, rich in fats and of offensive smell; in some cases associated with gastric and duodenal ulcers, blood was detected (dogs 501 and 544). In spite of the loss in weight, the animals were always active, never having shown signs of apathy or asthenia. Their coats and fur were covered by a greasy secretion.

Under the experimental conditions stated, ligation of the pancreatic ducts in the dog brought about a loss in weight and various organic and metabolic disorders. These results were demonstrated by quantitative changes in the concentration of certain blood constituents and by fatty infiltration of the liver. The blood imbalance became manifest through (a) a drop of serum proteins; (b) decrease of the total plasma cholesterol together with a relative rise of free cholesterol (or a fall of ester cholesterol); (c) decrease of the plasma phospholipids; (d) drop in plasma prothrombin; (e) increase of the alkaline phosphatase activity of serum.

[1]Due to lack of space, the protocols of each individual dog have been omitted.

The *loss in weight* was notable within a few days after the operation and became more pronounced during the days in which no lipocaic was administered. This weight loss cannot be due to anorexia as the animals were provided with abundant rations and had excellent appetite; it is caused more likely by a disorder of the fat and protein absorptions brought about by the absence of pancreatic enzymes in the intestine. This condition is partly shown by the increase in volume and frequency of stools very rich in fats.

A fall in serum proteins became evident between the 28th and 37th days after the operation (dogs 621, 661, and 681) and can be considered as an indication of absence of the pancreatic proteolytic enzymes in the intestine. As time passed, the hypoproteinemia became more marked, except in those cases in which the casein hydrolysate was injected (dog 671).

A decrease of total cholesterol—sometimes preceded by a slight increase (dogs 501 and 526)—was seen in all cases and became more accentuated in the course of time. It was already apparent on the 17th or 28th day after operation, but the intensity and speed of development of this symptom varied: the decrease value was 58.3 per cent on the 51st day in dog 501; 64.3 per cent on the 56th in dog 503; 65.7 per cent on the 106th day in dog 524; 46.3 per cent also in the 106th day in dog 526; and 68.9 per cent on the 161st day in dog 544.

Parallel to this decrease of total cholesterol there was a relative increase of free cholesterol (Chart 2); this is shown in the relation $\frac{\text{Free cholestrol}}{\text{Total cholestrol}}$, the value of which—according to our experiments—remains fairly constant under normal conditions (29.8–31.5%).[1]

This index underwent more modifications as time passed, even when there was a decrease of the total concentrations of total and free cholesterol. The quantitative variations differed according to the animals: after 51 days, it was 62.3 per cent of the initial value in dog 501; 71.5 per cent after 56 days in dog 503; 52.4 per cent after 106 days in dog 526;

[1]F/T% means the percentage of free cholesterol with reference to total cholesterol.

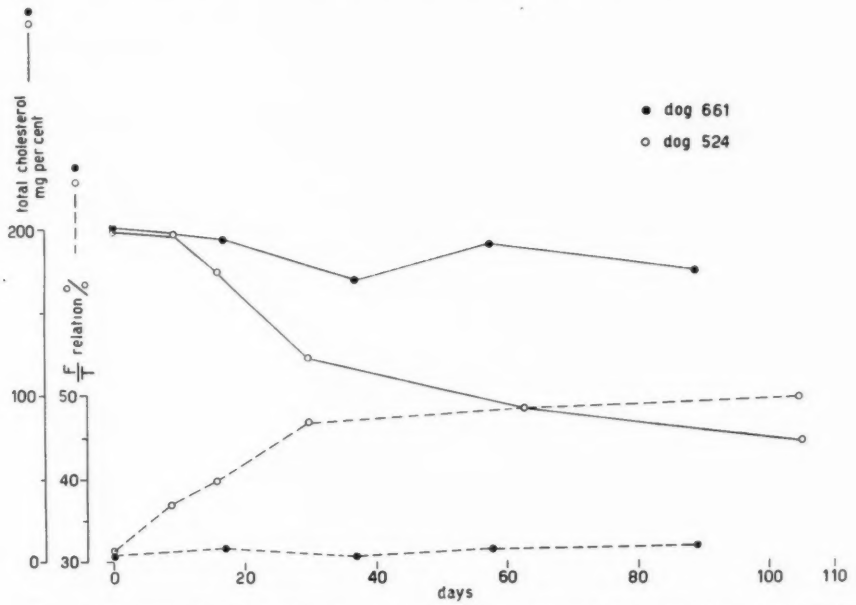

Chart 2. Decrease of total cholesterol and relative increase of free cholesterol in the untreated animals. This is expressed by the free to total cholesterol relation, the value of which remains fairly constant under normal conditions (29.8 to 31.5%) and in the dogs treated with lipocaic (dog 661).

59.7 per cent also after 106 days in dog 524; and 109 per cent after 161 days in dog 544.

The *decrease of phospholipids*—sometimes preceded by a slight increase (dogs 501 and 526)—was more or less slow, yet constant and always parallel to that of cholesterol (Chart 3). After 51 days the value of this fall was equivalent to the 28 per cent of the initial value in dog 501; after 56 days, to 55.3 per cent in dog 503; after 106 days, of 48.5 per cent in dog 526; after the same number of days, of 55 per cent in dog 524; and after 161 days, of 58.4 per cent in dog 544.

The *fall of prothrombinemia* was an early feature and parallel to the aforesaid blood constituents. In dog 544 this decrease reached the figure of 65.2 per cent of the initial value on the 20th day after operation and in dogs 524 and 526, of 38.7 and 56.8 per cent respectively, on the 106th day.

The *increase of the alkaline phosphatase activity* of serum also appeared early and it rose during the course of time, up to figures 22 times higher than the initial value (dog 501).

Preventive action of the pancreatic extract. Different doses of the extract prepared according to our technique were studied in dogs 661 and 581 with the view of studying its capacity for preventing the appearance of the aforementioned blood changes. Capsules were administered to dogs as soon as appetite reappeared, viz., on the 2d and 3d days after duct ligation. Daily doses equivalent to 75 grams of fresh pancreas (5 capsules) proved capable of maintaining within normal limits, during 3 months, the animal's weight, cholesterolemia, free to total cholesterol relation and lipoidic phosphorus, but not prothrombinemia. The latter, though never reaching hemorrhagic levels, always showed itself irregularly variable.

An interesting feature was observed in the case of phosphatase: it rose during the first days, but it began to fall after the 17th day, to return to normal on the 58th day. This evolution should be compared to that of untreated dogs, in which increase of phosphatase activity is a constant feature (Chart 1).

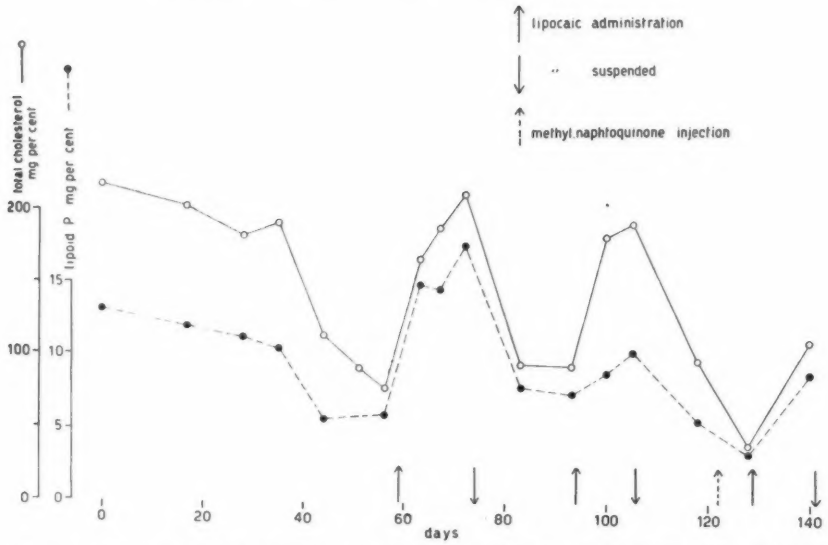

Chart 3. The decrease of phospholipids always parallel to that of cholesterol. The daily administration of 5 capsules of lipocaic produces an increase of total cholesterol and phospholipids. The modifications are unquestionably due to the effect of pancreatic extract administration, because figures show that as soon as it is stopped, the blood changes recur; moreover, they again disappear when treatment is started anew.

A dose of less than 5 capsules was incapable of maintaining a normal blood picture (dog 681). A subsequent increase to 5 capsules daily, restored altered values to normal, with the exception of blood proteins and prothrombin; phosphatase did not return to its initial value, yet decreased to figures close to it.

The administration of 5 capsules daily of the Y preparation proved to be more efficient than 3 of our extract daily, yet less so than 5 of the latter, as shown by the free to total cholesterol relation.

Corrective action of the pancreatic extract. Experiments were also carried out to see whether the extract was capable of correcting the dysfunctions caused by ligation of the pancreatic ducts. This experiment was done by administering the substance 58, 112 and 161 days after the operation (dogs 503, 562 and 544, respectively), when the values of cholesterol, phosphorus, and prothrombin in blood were low and the free to total cholesterol relation increased in the aforesaid proportion.

The daily administration of 5 capsules of our preparation brought about an increase of the total cholesterol, phospholipids, and prothrombin, together with a decrease of the free to total cholesterol relation. When the administration was started on the 60th day after operation the preoperative levels were exceeded on the 13th day after the treatment was commenced; yet if the administration of the extract was begun 113 and 132 days after surgical interference, this rise did not take place until after 13 and 20 days, respectively, after the administration was started. Prothrombin behavior was irregular; dog 524—in which treatment was started latest of all—showed greater increase than that which appeared in dog 526.

The modifications are unquestionably due to the effect of pancreatic extract administration, because figures show that as soon as the extract is stopped, the blood changes recur; moreover, they again disappear when administration of the extract is started anew (Chart 3).

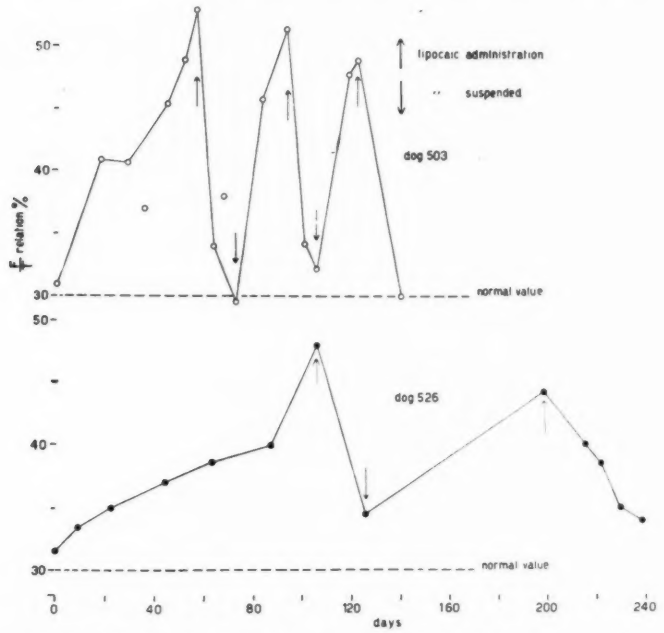

Chart 4. The increase of the free to total cholesterol relation is prevented or corrected by the administration of lipocaic.

As time passes the response to the oral administration of pancreatic extract becomes both less regular and not so marked (Chart 4). Though there is an improvement, in spite of longer treatment, the complete recuperation to preoperative levels is never achieved.

Shortage of material prevented us from pursuing these tests for very long periods; however, we suggest the possibility that more prolonged treatment or larger doses may bring about complete corrective action. With reference to the latter, it is worth mentioning that at the end of 8 days, the daily administration of 10 capsules of our extract (equivalent to 150 grams of fresh pancreas) failed to exceed the absolute increase of blood cholesterol and lipoidic phosphorus obtained with 5 capsules daily; nevertheless, they improved the free to total cholesterol relation beyond all comparison, notwithstanding the fact that the administration was begun 193 days after duct ligation.

The study of the corrective action of lipocaic on blood hyperphosphatasemia (dogs 621, 671, and 681) shows that, together with cholesterolemia and phospholipemia, hyperphosphatasemia undergoes a marked decrease with the administration of adequate doses of our preparation.

The corrective action of the Y preparation on the blood changes was tested on dog 524. The administration was started 107 days after operation, and although employing doses similar to those of our preparation, it proved to be much less active. This striking occurrence with a substance manufactured by the same process as ours, was the result we believe of faulty technique. We learned that the temperature to which the extractive fluids was submitted during the concentration process was not controlled: thus the lessened activity, due to the thermolabile character of the lipotropic principle of the pancreas (14, 27).

Tests by systemic administration. Injected into dog 526 at the moment when biopsy of liver tissue revealed a large degree of fatty infiltration (Figs. 3 and 4) and an abnormal

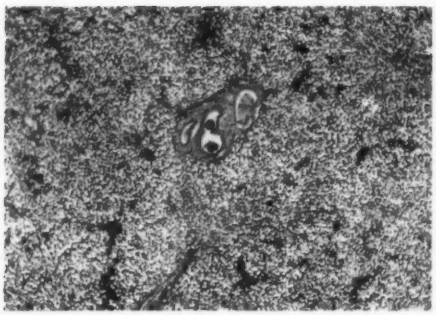

Fig. 1.

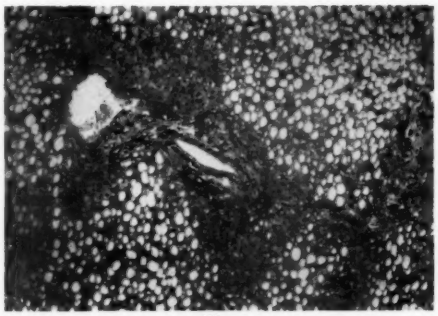

Fig. 3.

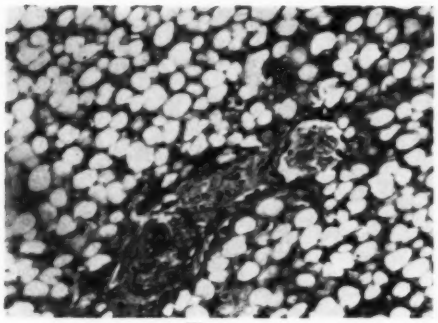

Fig. 2.

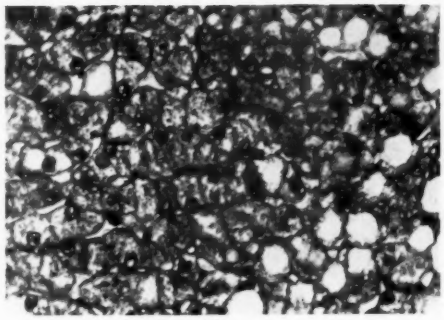

Fig. 4.

Figs. 1 and 2. Dog 503. Massive fatty infiltration of the liver. The cells of the trabeculae are deformed and round shaped owing to the presence of fat. Now and then 2 or 3 liver cells of normal appearance can be seen. There is no reaction of the connective framework. Free to total cholesterol relation, over 52 per cent.

Figs. 3 and 4. Dog 526. Liver biopsy performed on the 308th day of experiment and after 67 days without treatment. Marked fatty infiltration in the central trabeculae, though less than in dog 503. With more powerful lens, the central cells appear affected by cytoplasmatic disintegration, the nucleus remaining unchanged; others had undergone vacuolation and karyolysis (necrobiosis? fat-phanerosis?)

blood picture (310th day), our extract brought about a rapid increase of total cholesterol—together with an improved free to total cholesterol relation—and phospholipids but had no effect on prothrombinemia. Taking into account the short treatment (3 days) and the time since the ducts had been ligated, the response can well be considered as quantitatively higher than that given by an equivalent dose per os.

The Y preparation, tested on dog 524, also proved more active parenterally than by mouth.

We believe that the lesser efficacy of oral administration is due to a partial loss of the lipotropic principle in the intestine caused by both the anomalous absorption and accelerated intestinal transit seen in dogs with ligated pancreatic ducts.

We shall now discuss tests with two other preparations administered systemically, which we shall call X and Z.

One milliliter daily of preparation Z given subcutaneously to dog 621 during a fortnight, gave rise to an insignificant increase of total cholesterol, together with a higher free to total cholesterol relation and a decrease of phospholipemia; only prothrombin showed a significant improvement.

The daily subcutaneous injection of 4 milliliters of preparation X—started 13 days after oral administration with our extract, when cholesterol, free to total cholesterol relation and phospholipids in blood had become nor-

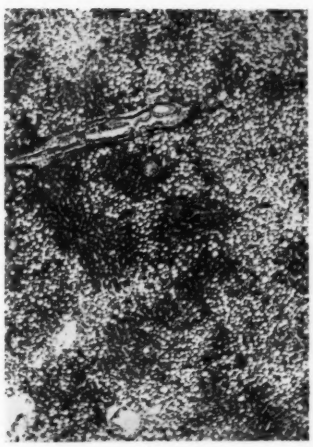

Fig. 5.

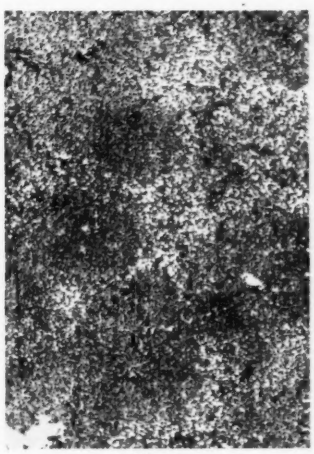

Fig. 6.

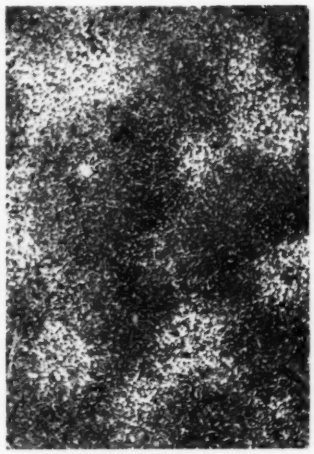

Fig. 7.

Fig. 5. Dog 544. Liver with perilobular fatty infiltration. The structure of the remaining cells of the lobule is totally unaffected. Free to total cholesterol relation, 52 per cent.

Fig. 6. Dog 524. Liver biopsy obtained after 20 days' treatment with systemic injection of lipocaic (230th day of experiment).

The hepatic structure is preserved; there is only a slight fatty infiltration of the peripheral cells of the lobules. Normal connective tissue. Free to total cholesterol relation, 37 per cent.

Fig. 7. Dog 524. Appearance of the liver at the end of experiment. The fatty infiltration is somewhat more pronounced than in Figure 6, and always of perilobular localization. Under a more powerful lens, the liver cells are seen with a normal nucleus and cloudy cytoplasm. Slight polymorphonuclear infiltration between the trabeculae. No cell necrosis. Free to total cholesterol relation, 41.5 per cent.

mal—caused these values to drop to abnormal levels at the end of 29 days of treatment, with an increase of blood phosphatase and maintenance of hypoprothrombinemia.

In view of the fact that subsequent administration of our extract corrected the altered values, those results can be attributed to the small activity (or total lack of it) of the preparations X and Z, at least in the doses used by us.

Complementary tests. The decrease of serum proteins in all dogs with ligated pancreatic ducts led us to investigate the possible relation between the hypoproteinemia and the other blood changes observed in these animals. Therefore, we used daily doses of casein hydrolysate intravenously, in amounts equivalent to 267 milligrams of nitrogen. The injection of the hydrolysate alone (dog 621) or as a complement to the oral administration of insufficient doses of our extract (dog 671) or of preparation Y (dog 621) always gave rise to an increase of proteinemia—which in some cases returned to normal—and of prothrombin. At the same time there was an adverse effect on the remaining blood components, as the cholesterol and lipoidic phosphorus figures dropped, while the free to total cholesterol relation and phosphatase activity rose.

Relation between fatty infiltration of the liver and blood changes occurring in dogs with ligated pancreatic ducts. Former papers by Chaikoff, Dragstedt, Ralli and others (4, 10, 12, 16, 17, 29) have shown the intimate relation existing between the fatty infiltration of the liver of dogs without pancreas or with ligated ducts, and the variations of cholesterolemia, the cholesterol esters and lipoidic phosphorus, to which we add those of blood phosphatase and prothrombin.

The following experimental facts prove that our pancreatic extract possesses lipotropic activity:

a. The absence of fatty infiltration was noted in the liver of dog 661 (Fig. 8) that received daily doses equivalent to 75 grams of fresh pancreas immediately after having had its pancreatic ducts ligated.

This result cannot be attributed to faulty operative technique, as at necropsy complete atrophy of the pancreas was found. Neither can the presence of a few Langerhans' islands on the covering omentum be considered as a cause, as the same thing was observed in every animal; moreover, a direct histological control was kept on dog 526 and an indirect one through the absence of diabetes in all animals. Only dog 550 showed a macroscopically identifiable pancreas (although somewhat smaller in size), but in this dog the accessory duct was found patent, thus explaining the lack of blood and liver changes.

b. The presence of fatty liver (diagnosed macroscopically) in untreated dog 501. The short time which elapsed between ligation of duct and the appearance of this lesion (51 days at the most) shows this case to be an early one, as Chaikoff and associates (24) say that in their experiments the minimum lapse of time was 12 weeks.

Comparing the blood picture of these two opposite experimental conditions (dogs 661 and 501) with that belonging to the dogs subjected to different treatment, and studying them with their respective microscopic pictures, it is easy to conclude that both the fatty deposit in the liver of dogs with ligated ducts and its mobilization by means of lipocaic can be followed through the variations of total cholesterol, free to total cholesterol relation, phospholipids and phosphatasemia. However, from the quantitative viewpoint this interrelation is so variable in the different animals that we were unable to establish the minimum effective dose of lipocaic.

Free cholesterol and free to total cholesterol relation. Dogs with ligated pancreatic ducts show total hypocholesterolemia, together with a rise in the relative concentration of free cholesterol (or as some authors describe it, a decrease of the cholesterol esters) as shown by an increase of the free to total cholesterol relation. Already described by other investigators (10, 29).

We were able to prevent or correct this alteration by the daily administration in doses of 75 grams of our extract of fresh pancreas, given both by mouth and systemically.

Broadly speaking both indexes have a parallel evolution under the influence of the alternatives of lipotropic treatment, although their quantitative response is inversely related to the time elapsed between the ligation of the ducts and the beginning of treatment. This would seem to suggest that, as time passes, the liver injury caused by the operation, becomes progressively refractory to the lipotropic action of the extract.

However, if we compare the histological pictures of our dogs' livers with the free to total cholesterol relation, it seems possible to establish a gross analogy between the value of the latter and the different degrees of fatty infiltration. In fact, the progression of the fatty infiltration shown in the photomicrographs is parallel to the increase of the corresponding values of the free to total cholesterol relation, to wit:

Fatty infiltration:
Photomicrographs No. $1>3=5>7>6$
F/T relation %: $+52>52.5=52.4>41.5>37$

Therefore, in these dogs, a free to total cholesterol relation equal to or higher than 50 per cent can be taken as an index of an intense fatty infiltration of the liver.

The positive response to the lipocaic's lipotropic action has been pointed out as characteristic of fatty livers rich in cholesterol (22). As McHenry suggested, such an antifatty liver factor may be somehow related—in a manner as yet unknown—with the cholesterol metabolism.

It is also possible that the return to normal of the free to total cholesterol relation may be due to the hepatocyte having regained its capacity to esterize free cholesterol which had been affected during the process of fatty infiltration. Thannhauser and Shaber say that the fall of the cholesterol esters (*Estersturz*) seen in cases of liver injury is caused by an alteration in the liver cell's capacity to esterize free cholesterol with fatty acids. However, Gardner and Gainsborough, Bürger and Habs, and other investigators, have challenged the idea of considering the liver as the specific and indispensable center of cholesterol esterification in view of the fact that this function is still present—and even increased—in hepatectomized animals (20).

Phospholipids. As stated before, after the pancreatic ducts are ligated there is a fall in the blood content of phospholipids parallel to that of cholesterol; however, these figures rise and even become normal after lipocaic administration. This fall has also been reported by Chaikoff (4, 5, 16) in depancreatized dogs treated with insulin or in others with ligated pancreatic ducts; it was considered as an index of a decrease of the plasma choline because the latter is found entirely combined as phospholipid (31, 32).

According to this author (5) the decrease in circulating choline is not due to its absence in the diet, but to a lack of the lipotropic factor of the pancreas which has an enzymatic character and therefore acts through setting free the methionine present in the food proteins. Once absorbed, methionine is transformed into choline, i.e., the real lipotropic agent.

The relation existing between choline and methionine has been indisputably proved by du Vigneaud (13, 33) in the rat, rabbit and man, and by McKibbin in the dog. These authors showed that choline arises from methionine, thanks to the labile methyls of the latter's molecule. The administration of pancreatic extract—source of Chaikoff's enzymatic factor—would allow the methionine of foods to be used as lipotropic agent, with the resulting choline synthesis and increase of plasmatic phospholipids.

Our results, although confirming Chaikoff's in the matter of the phospholipemia variations brought about by providing or withdrawing administration of pancreatic extract to dogs with ligated pancreatic ducts, do not agree with his theory of the rôle of methionine in this process. This was shown by the fact that the injection of casein hydrolysate had no lipotropic effect, as witnessed by the values of cholesterol, phospholipids, and prothrombin in blood. This statement of ours is made with reservations, as we were unable to assay quantitatively the methionine present in the hydrolysate.

Alkaline phosphatase. After the pancreatic ducts had been ligated, phosphatasemia increased in every animal. Bearing in mind that the rise of alkaline phosphatase activity of blood has been taken as a sensitive index

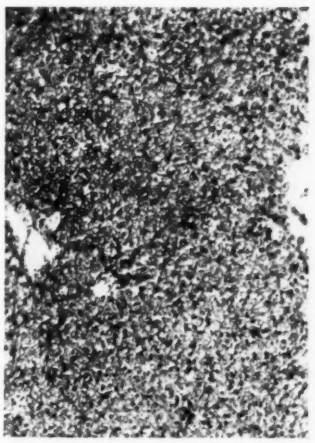

Fig. 8. Dog 661. No fatty infiltration. Slight granular disintegration of the liver cells with nucleus of normal appearance. Free to total cholesterol relation, 32 per cent.

of functional or minimal biliary obstruction (3), it is possible to understand the marked and progressive hyperphosphatasemia in both dogs not having received lipocaic (dog 501), and in those in which the changes in the blood values of cholesterol and phospholipids pointed to the presence of a fatty infiltration of the liver.

In fact, the fatty accumulation in the liver can be considered as equivalent to a moderate biliary obstruction, which would explain the rise of phosphatasemia to levels lower than those seen in total obstruction, yet higher than the ones found in hepatosis (3). This statement is further supported by the fact that lipocaic treatment decreases hyperphosphatasemia, but not always improves prothrombin figures. The latter occurrence speaks more in favor of a liver cell injury.

According to our observations on cholecystectomized dogs (3), the meaning of the initial hyperphosphatasemia seen in dog 561 is of different origin. The absence of fatty infiltration in this animal's liver suggests that in this case the transitory increase of blood phosphatase is due to a slight functional biliary obstruction caused by surgical interference. If it is remembered that the accessory pancreatic duct opens into the duodenum at the very level at which the common bile duct be-

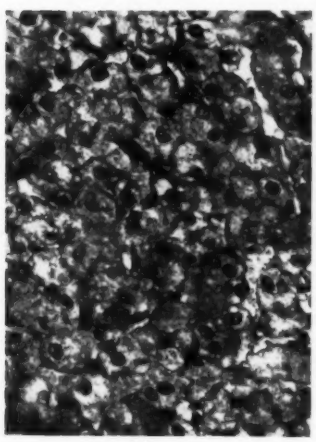

Fig. 9.

Fig. 10.

Fig. 9. Dog 671. Appearance of the liver after 51 days' treatment with adequate doses of lipocaic. No fatty infiltration. Hepatocytes are slightly round-shaped and swollen. Normal nucleus and cloudy cytoplasm in the process of disintegration (albuminoid degeneration). Some small necrotic foci in which the nucleus of cells has disappeared. Free to total cholesterol relation, 33.4 per cent.

Fig. 10. Dog 550. Normal appearance of the liver. Necropsy of this animal showed the persistence of the pancreatic duct accessory. Free to total cholesterol relation, 29 per cent.

comes intraparietal, this operative trauma will explain why there is a return to normal of phosphatasemia after 50 days, just as in cases of cholecystectomized dogs. This effect should also be present in untreated dogs, but when the time comes for it to disappear, this does not take place owing to the fatty infiltration of the liver.

If our conception of the problem is correct, the return to normal of phosphatasemia is a more accurate index for revealing the disappearance of the fatty infiltration of the liver under the action of lipotropic preparations, than that of cholesterolemia, free to total cholesterol relation and phospholipemia. The disappearance of the infiltration should take place at least 50 days after the duct ligation. This fact agrees with the observation that phosphatase activity does not entirely return to the initial level at the time when the other blood components have become normal under the effect of the administration of our extract (dog 544, 51st day).

We believe that the persistence of a marked hyperphosphatasemia in dogs with pancreatic ducts ligated more than 50 days before, must be considered as an additional index of fatty infiltration of the liver.

Prothrombin. Our results show that in the dog, the ligation of the pancreatic ducts causes a liver injury revealed by a fall in the prothrombin concentration of the blood. This decrease cannot be attributed to a lack of vitamin K intake, as treatment with 2-methyl 1–4 naphthoquinone did not improve the hypoprothrombinemia in accordance with the doses given. Instead, the subsequent administration of lipocaic proved to be far more effective.

The effect on hypoprothrombinemia of pancreatic extract administration became more evident in the treatment of early cases, but only in 2 of the 9 dogs we studied was it found possible to increase it to normal figures. In the 7 others, the response was either variable or never reached the subnormal concentrations, even though there was a return to normal of hypocholesterolemia and phospholipemia.

The persistence of hypoprothrombinemia after the normalization of the other blood

changes following the administration of the lipotropic extract and the shortlived initial fall in the prothrombin of dogs without fatty liver (dogs 661 and 550) seems to indicate that the variation of this blood principle is due, not only to the presence or lack of fatty infiltration of the liver, but to some other cell injury that lipocaic does not repair altogether. Former experiments of ours (3) showing prothrombinemia as a more sensitive test for detecting the functional alteration of hepatocytes, undoubtedly support this assertion.

Prothrombin increase after an injection of casein hydrolysate (dogs 621 and 671) appears to suggest the existence of a certain relationship between the hypoprothrombinemia and the protein deficit; however, further research is required on this point.

Proteins. We have already remarked that the variations and response of proteinemia toward lipocaic administration are independent of those of the other blood components, and vice versa.

The use of pancreatic extract as a corrective and preventive measure caused serum proteins to decrease both in animals treated early and in those untreated; moreover, this decrease was unaffected by lipocaic administration. These results suggest that hypoproteinemia probably has its origin in deficiencies in protein digestion in the intestine brought about by ligation of the pancreatic ducts. In our experiments, the results of investigations with casein hydrolysates dismiss the possibility of hypoproteinemia as a source of fatty infiltration of the liver. Evidently in dogs with ligated pancreatic ducts, proteinemia and its regulating factors have no influence on the disorders of lipid metabolism and their repercussion on liver function.

With reference to the apparent potentiation of fatty infiltration of the liver by injections of casein hydrolysate, amino acid mixtures, and glucose, we cannot offer any plausible explanation. We believe that more purified preparations should be used, in order to exclude the possibility of a toxic action by foreign substances.

Liver changes brought about in the dog by ligation of the pancreatic excretory ducts. Macroscopical and microscopical examinations of the liver show that in the dog ligation gives rise to a pathological fatty infiltration of said organ. Is this lesion an exaggeration of normal processes? It does not seem to be so, as the said infiltration produces blood changes which reveal a considerable degree of liver injury.

Lipocaic administration corrects the liver infiltration provided treatment is started early; the later it is begun, the less pronounced is the improvement, thus a certain degree of liver injury remains.

A study of histological sections of the livers indicated that the functional disorder resembles that of a lesion with all the appearances of the reversible type. In the treatment of later cases, the impression remains that under more prolonged administration of the extract, the function of the liver eventually becomes normal. With reference to this, one should bear in mind the higher lipotropic efficacy of duplicating the effective minimum dose (dog 554, 193rd day) and of systemic administration.

A point worth stressing is the presence of a type of lesion (Fig. 9) in which the cytoplasma of the hepatocyte appears cloudy and disintegrating (albuminoid degeneration); there are also some necrotic foci and karyolysis. From the pathological viewpoint, albuminoid degeneration is considered as an alteration of the cell's proteic contents and it is often associated with a degenerative fatty infiltration (38). In this case (dog 671) such a lesion would explain the persistence of hypoprothrombinemia after the return to normal of cholesterolemia, free to total cholesterol relation, and phospholipemia, following the administration of pancreatic extract.

We are unable to tell to what extent the pursuance of treatment will influence the return to normal of altered liver function and cell architecture. This subject requires further study.

Glycemia behavior. We have purposely left the subject of glycemia to the end of our discussion as it is our opinion that glycemia is not influenced by the fatty infiltration process in dogs in which the pancreatic ducts have been ligated. In all cases blood sugar remained within normal limits until the end of the ex-

periment, even when the experiments lasted as long as 13 months and 17 days. This confirms the assertion that ligation of the pancreatic ducts causes a more or less complete atrophy of the acinous tissue of the organ, yet does not affect Langerhans' islands; in other words, the functional activity of the remaining tissue is enough for the maintenance of normal glycemia (Szobolew, 34).

Strictly speaking, the values of blood sugar stayed at a level very near the lower margin of the normal range (70 mgm.% according to the method used). Therefore it seems possible that the liver function or the alteration of the metabolic processes of carbohydrates and fats bears influence on the regulation of blood sugar.

As it was impossible to recognize macroscopically the pancreas of our dogs—with the exception of that of dog 550, where it was found that the accessory duct had not been ligated—we made histological sections of the piece of omentum interposed during operation between the pancreas and duodenum. This structure was found to have acquired the appearance of a fibrous cord, adherent to the duodenum. Under microscopic examination, these sections showed fibrous tissue, in which islands of cells, of the Langerhans' appearance, could be seen. The persistence of these cells may explain the absence of diabetes in our animals; however, this statement is made with all due reservations owing to the fact that we did not identify the alpha cells by means of the specific staining method.

We do not wish to bring this commentary to a close without stressing the efficiency of the method for ligating the excretory pancreatic ducts in order to produce fatty infiltration of the liver of dogs. The failure of some research workers to achieve this must be attributed to the difficulty of localizing and ligating the pancreatic accessory duct. In our experiments only one dog (No. 550) failed to develop a fatty liver in spite of not having been treated with lipocaic, and necropsy showed that the accessory duct was still present and the gland was almost unaffected. This fact explains the normal blood picture and the normal liver architecture which is present in this dog (Fig. 10).

SUMMARY

1. The original technique of Dragstedt and associates for preparing a fat-free pancreatic extract with lipocaic activity, has been modified by us. This modification entails the elimination of ether in the separation of lipids and allows the recuperation of the alcohol used for gland extraction.

2. The extract thus obtained contains no fats, cholesterol or reducing sugars and lacks tryptic activity. Its average content of total nitrogen is equivalent to 10.31 grams per cent, and that of mineral salts to 17.2 per cent of dry extract.

3. Studies are detailed concerning the organic changes brought about by the ligation of the pancreatic excretory ducts in dogs. These animals were fed on bread, milk, meat and sugar. The fact is confirmed that sooner or later, the operation causes the atrophy of the pancreas and the fatty infiltration of the liver.

4. The blood changes consisted in fall of the absolute concentrations of total cholesterol, phospholipids, prothrombin and proteins, together with an increase in the alkaline phosphatase activity and in the relative concentration of free cholesterol. The intensity and rapidity of appearance of these changes vary according to the dogs; however, by the 60th day after operation they had reached levels purporting a fatty infiltration of the liver.

5. The activity of the pancreatic extract prepared according to the expounded technique was studied in relation to its capacity of avoiding or correcting the organic alterations mentioned in the text.

The results were as follows:

a. The oral or systemic administration showed an increase of total cholesterolemia and phospholipemia, together with a fall of the phosphatasemia and relative concentration of free cholesterol, in all cases exhibiting changes of these values owing to the fatty infiltration of the liver. Hypoproteinemia did not respond to treatment and prothrombin did so in a very irregular fashion.

b. Extract administration, started 2 or 3 days after ligation of the pancreatic ducts, prevented the formation of a fatty liver in the 3 months during which the experiments lasted.

During that time the blood picture remained within normal limits, with the exception of proteinemia, which decreased as in untreated dogs. Blood phosphatase rose at first (the cause of this is discussed) but returned to normal after 50 days.

c. From the quantitative viewpoint, the response to the corrective action of the same amount of extract was inversely proportional to the time elapsed between the duct ligation and the onset of treatment.

6. In both the animals treated late with the extract and those protected by early administration, the suspension or renewal of treatment can be followed through the fluctuations of the total cholesterolemia figures, the relative concentration of free cholesterol, and those of phospholipemia and phosphatasemia. Even in the most chronic cases, the effect of the extract is evident, although response appears later and treatment has to be carried out longer.

7. The minimum daily dose of pancreatic extract capable of preventing or correcting the aforesaid changes is one equivalent to 75 grams of fresh pancreas.

8. Systemic administration is more effective than the oral route. This is probably due to the fact that in the former the lipotropic principle is wholly absorbed.

9. The relation $\frac{\text{Free cholesterol}}{\text{Total cholesterol}}$ was always higher than 50 per cent in cases in which an intense fatty infiltration of the liver could be seen both macroscopically and microscopically.

10. For judging the disappearance of the excess of liver fat through the action of the lipotropic preparation, the return to normal of phosphatasemia is a more accurate index than that of total cholesterol, the relation $\frac{\text{Free cholesterol}}{\text{Total cholesterol}}$, and lipoidic phosphorus.

11. The proteinemia modification appears to bear no relation to the fatty infiltration of the liver, as it does not respond to pancreatic extract administration and its return to normal through an injection of casein hydrolysate is not accompanied by a parallel improvement of the other blood changes.

12. The irregular response that plasma prothrombin has shown in some cases after lipotropic treatment, seems to indicate that its variations are not solely subordinated to the accumulation or mobilization of the infiltrating fat. The persistence of hypoprothrombinemia when all the other blood components have returned to normal levels, suggests that a small amount of injury of the liver cells still remains which cannot be corrected altogether by the lipotropic principle of the pancreas.

13. Although a certain relation exists between the value of the relative concentration of free cholesterol in the blood and the degree of fatty infiltration of the liver, it is impossible to establish a quantitative relation between the extract's activity and the variations of cholesterolemia, phospholipemia, and phosphatasemia. This difficulty is due to individual differences in the animals and to the intensity of the response to pancreatic extract as influenced by the length of time elapsed between ligation of the pancreatic ducts and the moment at which the lipotropic treatment was started.

14. In all cases, and although total atrophy of the pancreas was found at necropsy in every case, blood sugar remained within normal limits. This absence of diabetes appears to be related to the persistence of certain cell formations in the omentum, which have all the characteristics of the Langerhans islands.

15. Of the 10 dogs in which the pancreatic ducts were ligated, only in one did this operation not give rise to either an atrophy of the pancreas or fatty infiltration of the liver. This animal was not given extract. The postmortem examination showed that the accessory duct was patent.

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PATELLECTOMY

A Simplified Technique

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THE increasing popularity of patellectomy together with the recognition of more frequent indications for the operation justifies the report of a simplified technique.

The general indication for patellectomy is a condition of the patella which impairs function of the knee joint or produces continued trauma to the joint surface and is painful. Patellectomy has been recommended for the following conditions: severe hypertrophic arthritis, traumatic arthritis, chondromalacia, osteochondritis dissecans, degenerative chondritis and old malunited fractures of the patella.

The technique to be described is not applicable in acute fractures or in old fractures of the patella which have not been repaired. The decision to remove the patella should be made before the operation as a capsular incision precludes use of this method. Sir Robert Jones was largely responsible for the split patellar approach to the knee joint. This bisection of the patella is not recommended except when it is to be followed by excision.

From Campbell Clinic, Memphis, Tennessee.

Approach may be made either through a transverse or an anteromedial parapatellar incision. The skin and subcutaneous tissues are reflected, thus exposing that portion of the extensor mechanism covering the anterior surface of the patella. The quadriceps expansion overlying the patella is then incised longitudinally in the midline. The incision is prolonged into the patellar and quadriceps tendons for the distance of 1 centimeter. The knee is flexed slightly and maintained in this position. The patella is grasped with towel clips on its medial and lateral sides in order to steady it while the operator sections it longitudinally with a saw (Fig. 1).

Care is taken to avoid introducing bone dust into the knee joint by careful cleansing of the wound just prior to completion of the patellar section. The patella is then elevated with the

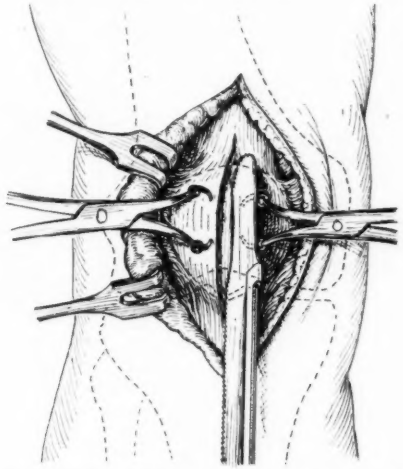

Fig. 1. Anterior surface of patella has been exposed and the bone is being divided with a saw.

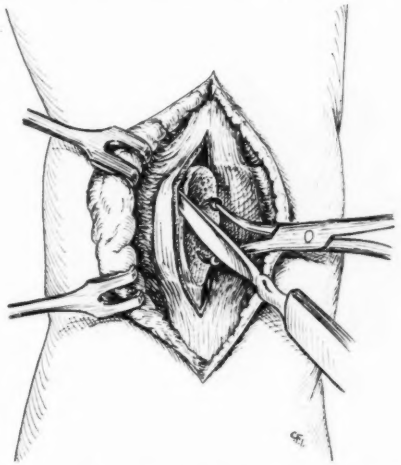

Fig. 2. Half of the patella is being enucleated from the extensor mechanism.

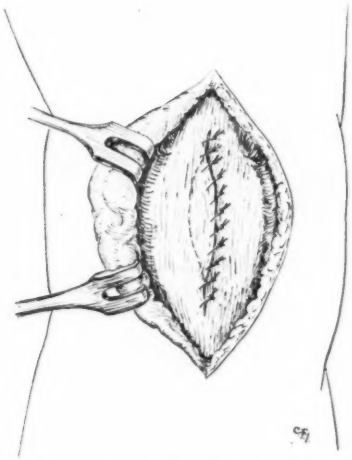

Fig. 3. The defect in quadriceps mechanism has been closed by plication.

towel clips in order to avoid traumatizing the cartilaginous surface of the femoral intercondylar notch as the section is completed with the saw or an osteotome.

One half of the patella is then grasped with a towel clip and positioned in such manner that the quadriceps expansion can be separated from the anterior surface of the patella by sharp dissection (Fig. 2). The other half is removed in like manner.

The anterior compartment of the knee joint can now be visualized for exploration or any additional surgery that may be indicated.

In closure of the extensor apparatus, the edges may be simply approximated or imbricated with interrupted nonabsorbable sutures of cotton or silk (Fig. 3). The remainder of the wound is closed in layers in the usual manner.

In methods of patellectomy which require a transverse closure of the extensor mechanism, there is marked tension on the suture line making early active contraction of the quadriceps and flexion of the knee joint hazardous. The technique of patellectomy described does not produce a defect in the extensor apparatus or divide the capsule on either side of the patella. There is minimal tension on the suture line during active extension or flexion of the knee which permits immediate quadriceps setting exercises and early active motion in the knee joint.

COMMENTS

1. A simplified technique for patellectomy is described. This method has been employed in 10 cases.

2. The expansion of the quadriceps mechanism and capsule of the knee joint are not damaged.

3. Shortening of the quadriceps is not produced.

4. The defect in the quadriceps mechanism is minimal and can be closed in longitudinal direction.

5. Immediate postoperative quadriceps setting exercises and early active motion may be instituted without jeopardy to the suture line.

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PROGNOSIS IN CARCINOMA OF THE BOWEL

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THE desirability of doing end-to-end anastomosis when resecting carcinoma of the colon or rectum is now one of the standard topics for discussion at surgical meetings. This paper will summarize some of our findings and may help you decide the proper procedure for each case.

Nine years ago, we reported a method for the examination of surgically removed specimens of carcinoma of the colon and rectum (2). By this method the specimens are made transparent, so that lymph nodes as small as one-half low power microscopic field (× 100) can be identified easily. Full scale drawings of the specimens were made with accurate location of all of the lymph nodes. Microscopic sections of each node were made. We have studied about 325 specimens in this way and over 15,000 different nodes have been sectioned. The findings were similar in the entire series but this report will deal with the study of 200 of these patients who were operated upon 11 to 5½ years ago. Over 10,000 lymph nodes were sectioned in these 200 specimens.

Carcinoma spreads by direct extension, by the blood stream and through the lymph system. If the spread by direct extension is great, the tumor is apt to be fixed to other structures. In the colon, and especially in the sigmoid, such fixation is often due to inflammation, the tumor having extended much less than is at first imagined. This fact has justified the resection of contiguous organs. Spread by the blood stream seems to occur in 10 per cent to 15 per cent of operable cases as shown by Coller.

A study of our material has led to the conclusion that the lymphatic spread of carcinoma is primarily embolic, and that the nodes where cancer emboli lodge prevent further spread until the node is completely overwhelmed by carcinoma. Further embolic spread is through the collateral lymph channels, each new node involved tending to make a longer channel for a new embolus to travel. Spread from one node to another does not seem to be common, at least during the period when lesions are seemingly operable.

It is possible to reproduce this picture of spread through the lymph system experimentally (3). It is not difficult to insert a 27 gauge needle directly into the afferent lymph channels in a dog's mesentery. Similar injections can be made into lymph channels in a rabbit's ear or into lymph channels in the skin. We have made injections directly into as many as 14 different afferent lymph channels entering one node in a dog's mesentery. Many large afferent lymph channels break up into 2, 3 or more, short channels just outside of the node and then these short channels pierce the capsule to empty into different parts of the subcapsular space, or one of the short channels may empty into the lymph sinus of an adjoining node. In addition, there are usually several different anastomosing channels between the large afferent channels draining a given region of the bowel, and the channels draining into adjacent nodes on either side.

When a colored solution is injected into an afferent lymph channel of a dog's or rabbit's mesentery, using very low pressure, the solution will penetrate through the node without coloring all of it. The node seems to be divided grossly into separate anatomic units so that material from a given channel seems to drain to a limited part of the node. When pressure is used in the injection, the entire node will be colored before any dye appears in the efferent channel. If, instead of a colored solution, a suspension of carbon particles ½ to 1 μ in diameter, or of silica which is less than ½ μ in diameter, or a suspension of barium or carmine particles is used to inject into the afferent channel using very low pressure, a different picture is seen. The suspension of colored particles will partially fill its own com-

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partment in the subcapsular space (Fig. 1, *A*). If more pressure is used, the suspension will either overflow into the remainder of the node or it will enter the adjacent parts of the node through one of the short channels leading into a different part of the subcapsular space (Fig. 1, *B*). If there is much pressure, the node is soon a solid black and the suspension may pass into one or even two or three of the adjoining nodes through the short channels (Fig. 1, *C*). At the same time, it may back up one of the tributary channels emptying into the original channel injected, and it is often possible to get it to go through a retrograde anastomosing channel and come through another afferent channel into an adjoining normal node (Fig. 1, *D*). Even great pressure to the point of rupturing the walls of the afferent channels will not force any one of the fine suspensions through the node. If the animal is killed immediately or is allowed to live for a week and then killed, no sign of passage through any node is seen, either in transparent preparations or in microscopic sections. This experiment shows very graphically how, when a node is destroyed or blocked, the lymph drainage is rerouted through collateral channels, or by retrograde means, into a channel draining into a normal node. Carcinoma cells are many μ in diameter in contrast to these particles, which were all less than 1 μ in diameter. The normal system of collateral lymph channels, plus the demonstration of retrograde channels available when nodes are blocked, shows how much more likely spread of the large carcinoma cells is apt to be by collateral channels than by growth through lymph nodes.

A study of our surgical material has brought out the following facts:

1. Permeation of carcinoma through lymph channels was seen only when the lymph node central to the channel involved was already blocked with carcinoma.

2. Carcinoma metastases do not completely destroy the function of a node until all of the node is destroyed. This was shown in a surgical specimen of carcinoma of the breast. The lymph channels in the neighborhood of the tumor were injected with a suspension of carbon particles. The specimen was cleared and some of the lymph channels and several lymph nodes were seen to be outlined in black. This section shows how the carbon suspension could still flow into a node which contained a large metastasis. Most of the carbon is found in the normal part of the node; although, some of it penetrates a short distance along spaces between the cancer cells (Fig. 2).

3. Throughout the entire series a common pattern of lymph node metastasis was seen. The earliest metastasis was always found in the subcapsular space as in Figure 3. When the metastasis has grown larger than the small subcapsular lesion, the spread is by expansion around the subcapsular space and into the depth of the node. This expansion is usually accompanied by a thickening of the capsule especially over the area adjacent to the growth. There may be a more or less heavy layer of fibrous tissue between the cancer cells and the lymph cells. In many cases, there is so much interference with nutrition that we see a thick layer of fibrous tissue, a thin rim of live cancer cells within this, and necrosis in the center. Growth progresses until we see one or several large nodes, usually lying close to the main blood vessels, in which the lymphoid tissue is completely replaced by carcinoma. Groups of lymph nodes which are completely replaced by metastases tend to be found in certain regions. In specimens of carcinoma of the rectum and lower sigmoid, such nodes are usually located near the bifurcation of the superior hemorrhoidal artery (Fig. 4, No. 33779). In carcinoma of the breast, nodes about 1 inch below the brachial vein and along the lateral edge or just behind the pectoralis minor muscle are the ones most likely to be completely replaced by carcinoma. The group of heavily involved nodes is along the main or primary line of lymph drainage. Nodes involved below or lateral to these nodes are apt to be subcapsular lesions or ones which are obviously late metastases.

4. In no case has there been any evidence of penetration of carcinoma outside of the capsule of any node, except where there was a collection of large involved nodes lying tightly packed together. In cases in which this occurred, the superior hemorrhoidal artery or the main artery supplying the region of the nodes was blocked by pressure of the nodes. Several

of these nodes contained necrotic material.

5. In 7 cases, retrograde metastasis to lymph nodes was found below carcinomas of the rectum. In every one of these enough of the nodes central to the lesion were completely replaced by carcinoma to make us feel certain that there was a very marked obstruction to lymph flow, and the metastasis was by retrograde means (Fig. 4).

We will now study the 200 patients operated upon more than 5 years ago for carcinoma of the large bowel where there was a reasonable chance of cure (4). All of the surgical specimens were cleared and the lymph nodes were dissected under transillumination and the microscopically involved nodes were charted by the method described. The specimens used in this analysis were not always consecutive due to the work involved in the study of each one but were otherwise unselected except that the specimens from all fatalities were included. This results in somewhat higher mortality figures and lower 5 year survival rates.

These 200 patients represent an operability rate of approximately 75 per cent. Palliative resections for removal of tumor where known metastases could not be removed are not included in this group (Table I).

There is need for accurate anatomical location of tumors when discussing treatment of carcinoma of the rectum. The term "rectosigmoid junction" means different things to different surgeons. It can be located fairly accurately on proctoscopic examination. However, it is impossible to identify on a surgical specimen. Roentgenologists often consider it a region 2 or 3 inches in length. This study has demonstrated the very different prognosis, recurrence, and mortality rate in different regions of the colon. It seems to us that a new set of landmarks should be used. We have designated those carcinomas which are partially or completely below the peritoneal reflection as "extraperitoneal carcinoma

TABLE I.—200 CASES OF CARCINOMA OF THE COLON AND RECTUM

	Number	Per cent
Lymph node metastases present	125	62.5
Alive 5 to 10 years	114	57.0
Postoperative (hospital) deaths	19	9.5
Died 1 to 5 years—not carcinoma	8	4.0
Incomplete follow-ups	7	3.5

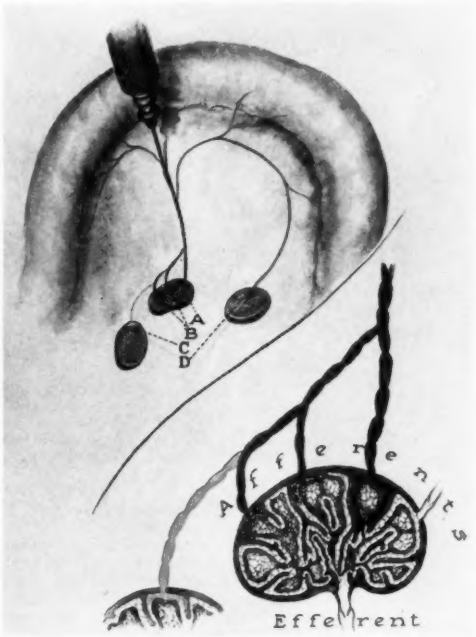

Fig. 1. Showing the manner of spread of a suspension of insoluble particles injected into a single afferent lymph channel.

of the rectum." There were 112 of these. Those lesions which are entirely covered by peritoneum, anteriorly, and which are below the promontory of the sacrum should be designated as "intraperitoneal carcinoma of the rectum." There were 41 of these. Fourteen were in the redundant loop of sigmoid above the promontory of the sacrum. (These last 2 —total of 55—will be grouped as one in this discussion as all findings were identical.) Fifteen were in the right colon, which included the cecum, ascending colon, hepatic flexure, and the first 3 inches of the transverse colon. Eighteen were in the left colon, which included all of the remainder of the colon to the redundant loop of the sigmoid.

One hundred and twelve tumors were partially or completely below the peritoneal reflection. There were 12 postoperative deaths and 4 had no follow-up. Only 26 of the 69 with node metastases were alive after 5 years (37.5 per cent), whereas 32 of the 43 without

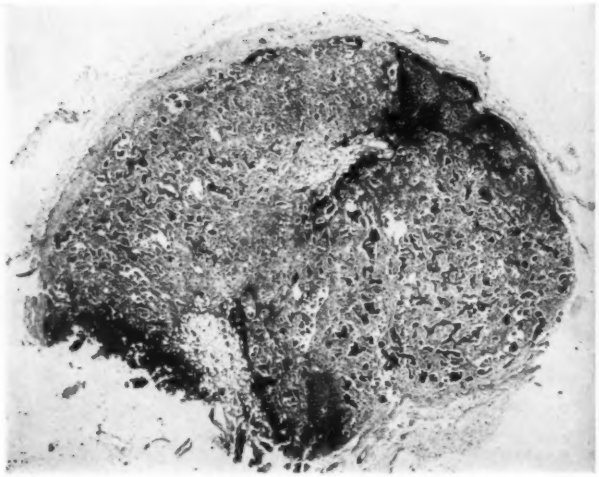

Fig. 2.

Fig. 2. Photomicrograph of lymph node almost completely replaced by carcinoma metastases. The normal parts are seen as dense, finely granular areas. A suspension of carbon particles was injected into the lymph channels in the neighborhood of the carcinoma of the breast. Most of the carbon is seen in the normal part of the node, although some of it penetrates a short distance along spaces between the cancer cells. A part of the lymph sinus which is involved with carcinoma also contains carbon particles. Two areas of fatty degeneration are seen.

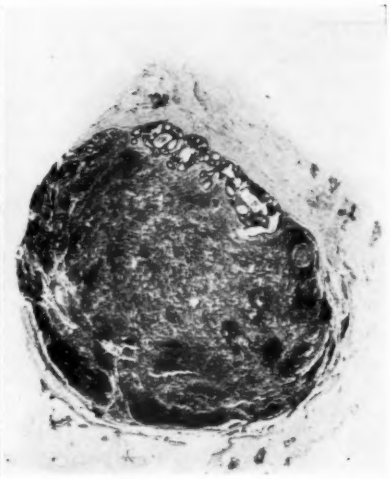

Fig. 3.

Fig. 3. Photomicrograph of a carcinoma metastasis which is confined to the subcapsular space. The thickened capsule lying over the region of the metastasis is clearly demonstrated.

node metastases were alive 5 years (74.4 per cent).

Of the 69 with node metastases, 30 or 43.5 per cent developed recurrent carcinoma in less than 5 years while only 5 or 11.6 per cent of the 43 without involved nodes developed recurrent carcinoma.

The incidence of local and liver recurrences in these low lying tumors is striking. If we subtract from the 69 with involved nodes the 16 patients who either died postoperatively in the hospital or were lost to follow-up, or those who died of other causes where there was no recurrent carcinoma, the figure for local recurrence will be more than 30 per cent and almost 20 per cent for liver recurrence.

TABLE II.—112 EXTRAPERITONEAL RECTAL CARCINOMAS

	Number	Per cent
Alive 5 to 10 years	58	51.8
Postoperative deaths	12	10.7
Lymph node metastases present	69	61.9
Of 69 with node metastases alive 5 years	26	37.5
Of 43 without node metastases alive 5 years	32	74.4

Fifty-five tumors were entirely above the peritoneal reflection. Fourteen were in the sigmoid and 41 were below the promontory of the sacrum. All findings were identical and these were grouped to save space. The favorable prognosis in this group, and especially in those without lymph node metastases (90 per cent), is striking (Table IV).

Twenty-seven of the 55 patients had obstruction resections performed. In many, the extraperitonealization of the resected area was done as described by David. In the more unfavorable cases, abdominoperineal resections were performed. This probably accounts for

TABLE III.—112 EXTRAPERITONEAL RECTAL CARCINOMAS

Recurrence	69 with node metastases		43 without node metastases	
	Number	Per cent	Number	Per cent
Local	16	23.2	2	4.6
Liver	11	15.9	2	4.6
Lung, bone, general	3	4.3	1	2.3
	30	43.5	5	11.6

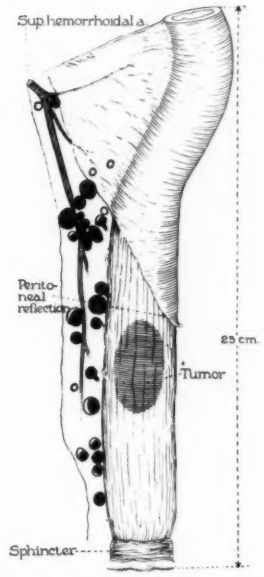

Fig. 4. Path. No. 33779. This is operative specimen showing metastases to lymph nodes 4 centimeters below the carcinoma. The amount of each node replaced by carcinoma is shown in black. The largest nodes are 4 millimeters or more in diameter. A mass of large necrotic carcinomatous nodes caused almost complete occlusion of the superior hemorrhoidal artery just above its bifurcation.

the fact that the results with obstruction resections were about the same as with the abdominoperineal resections. Of the fifty-eight, 18.1 per cent died of recurrence within 5 years, the recurrence rates being similar in the 2 types of operations. The low incidence of recurrence here contrasts sharply with the 43.5 per cent seen in tumors which are extraperitoneal.

TABLE IV.—55 INTRAPERITONEAL RECTAL AND SIGMOID CARCINOMAS

	Number	Per cent
Alive 5 years	36	65.4
Postoperative deaths	4	7.2
Deaths not due to carcinoma	3	5.5
Had no follow-ups	2	3.6
Had node metastases	36	63.3
With node metastases alive 5 years	18	51.4
Of 20 without node metastases alive 5 years	18	90.0
No follow-up	1	
Postoperative death	1	
Obstruction resections	27	
Alive 5 years	18	66.6

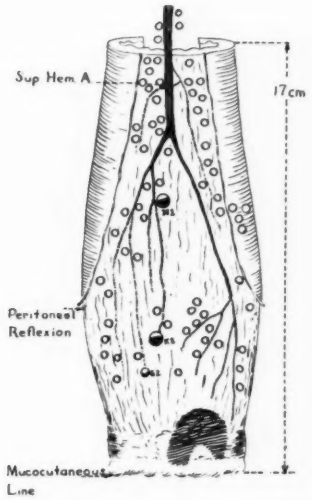

Fig. 5. No. 36682. A 64 year old man who had had symptoms for 2 months. This tumor was grade III Broder's and Duke's C. He developed a local recurrence in the hollow of the sacrum within 6 months. This finding of metastases in nodes high above low-lying tumors is not uncommon even when only a few involved nodes are present. This seems to re-emphasize the necessity for wide resection of mesentery even when there are no palpably enlarged nodes.

Resections of the 33 patients with carcinoma proximal to the sigmoid colon were done by several different surgeons. Twenty-one had lymph node metastases (63.6 per cent). Twenty were alive 5 or more years (60.6 per cent).

Fifteen were in the right colon; all had ileotransverse colon anastomoses at the time of resection. Thirteen, or 86.6 per cent, of these had metastases to nodes and, in spite of 3 postoperative deaths and 1 lost to follow-up, 9 were known to be alive after 5 years (61.5 per cent). These operations were performed before the era of chemotherapy; therefore, the operative mortality in this group would be lower at this time.

Eighteen tumors were in the transverse or descending colon. Only 8 had node metastases

TABLE V.—RECURRENCES IN 55 INTRAPERITONEAL TUMORS

	No. patients	Per cent
Local	2	3.6
Liver	6	10.9
Lung or general	2	3.6
Total	10	18.1

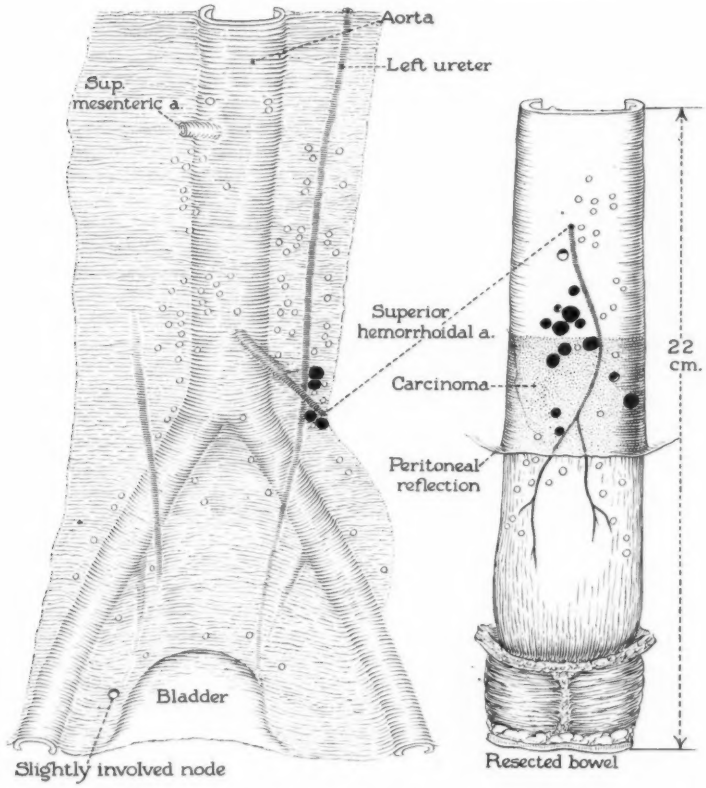

Fig. 6. No. 41772. Seventy-two year old man who had had symptoms for 4 months. The surgical specimen contained 46 lymph nodes. Fourteen of these contained metastases. He died of pneumonia. The autopsy specimen contained 114 lymph nodes. Four nodes above and one node just lateral to the field of resection contained metastases. This is an example of metastasis laterally along the levator ani muscle as well as upward along the superior hemorrhoidal artery. In spite of a very large tumor, the lymphatic metastases were localized to an area which could have been resected.

(44.4 per cent). This is the lowest incidence of involved nodes seen. Five of these 8 died of recurrence within 5 years. Only 3 of the 8 lived 5 years (37.5 per cent) in contrast to 80 per cent of those without involved nodes. All of these had obstruction resections. There were no postoperative deaths and one was lost to follow-up. This suggests that resection in this area has been too conservative.

TABLE VI.—15 TUMORS OF RIGHT COLON ALL WITH ILEOTRANSVERSE COLON ANASTOMOSES

	Number	Per cent
Alive 5 years	9	60.0
Had involved nodes	13	86.6
With involved nodes, alive 5 years	7	53.8
Postoperative deaths	3	
Had no follow-up	1	

TABLE VII.—18 TUMORS OF LEFT COLON ALL OBSTRUCTION RESECTIONS

	Number	Per cent
Alive 5 years	11	61.1
Had involved nodes	8	44.4
With involved nodes alive 5 years	3	37.5
No postoperative deaths	0	
Of 10 without nodes alive 5 years	8	80.0

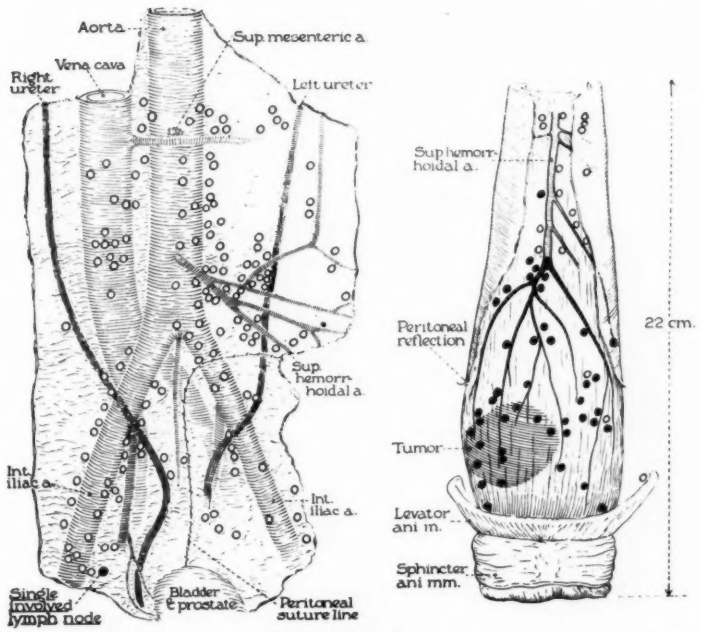

Fig. 7. No. 36303. A 63 year old man who had had symptoms for more than a year. Biopsy was made of this carcinoma 12 months before, but he had refused operation. The tumor was ulcerating and it had penetrated all coats of the bowel. Nodes were palpable in the hollow of the sacrum. Sixty-two nodes were found in the surgical specimen; 43 of them showed metastases. He died of a pulmonary embolus on the eighth postoperative day. One hundred sixty retroperitoneal nodes were examined microscopically. In spite of the extensive lymph node involvement, there were no metastases above the point of resection. The one node involved was about 1 centimeter lateral to the widest point of resection along the levator ani muscle.

The surgeon gave a guarded prognosis at the time of resection because of grossly enlarged lymph nodes in 55 of the 200 cases. Table VIII indicates the prognosis in those having palpably enlarged nodes proved to have metastases on microscopic section.

TABLE VIII.—55 OF 200 GIVEN GUARDED PROGNOSIS DUE TO LARGE NODES

Location of tumor	Alive 5–10 yrs.	Died 0–5 yrs.	Post-operative deaths	Recurrences			Deaths not carcinoma	Total patients
				Liver	Local	General		
Extraperitoneal								
With nodes	5	16	3	8	6	1	2	21
Without nodes	2	1					1	3
Below promontory								
With nodes	6	10		5	1	3	1	16
Without nodes	6							6
Colon								
With nodes	4	5	2	—	—	2	—	9
	23	32	5	13	7	6	4	55

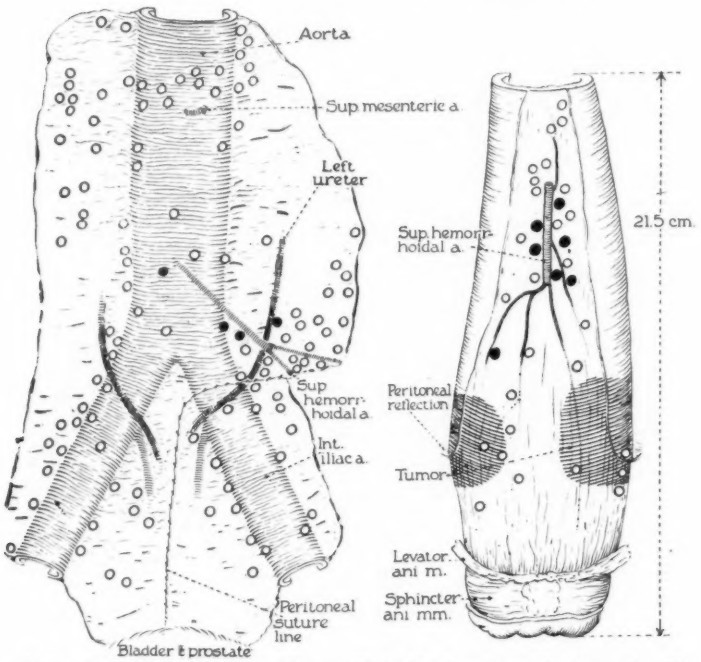

Fig. 8. No. 36642. A 72 year old man. He had had symptoms for 6 months. The surgical specimen contained 35 nodes and 7 of these contained metastases. He died of bronchopneumonia. One hundred eleven nodes were studied in the postmortem preparation; 4 contained carcinoma. The highest metastasis was in a node found at the junction of the inferior mesenteric artery and aorta.

Small scars ("grains of sand" nodules) were palpated in the liver in 11. These were too small and indefinite to be considered metastases. Eight lived 5 years. One died after operation. One developed a local recurrence and one who had no recurrence died of diabetes. These small lesions are usually almost of one size and the occasional operator should not be influenced adversely when they are found (Table IX).

Thirty-five of the 200 patients required resection of all or part of other structures because of firm fixation of the tumor (Table X).

TABLE IX.—POOR PROGNOSIS DUE TO SUSPICIOUS NODULES IN LIVER — 11

	Number
Alive 5 to 10 years	8
Died in less than 5 years	3
Postoperative death	1
Local recurrence	1
Diabetes, not carcinoma	1

Fourteen or 40 per cent of these patients were well 5 years. This figure would be higher today as 7, or 20 per cent, died after operation; this mortality would be favorably influenced by chemotherapy. Wide excision of structures adherent to the tumor is justified by these findings.

Seven patients having carcinoma below the promontory of the sacrum had metastases to lymph nodes distal to the tumor. Such metastasis occurs when there is lymphatic blockade. This finding re-emphasizes the necessity for extensive resection in those having enlarged nodes and large tumors.

Abdominoperineal resections of the rectum were performed in 140. Four of these were two stage resections. In 2, resections of other structures made a mass of tissue too large to pull through the pelvic outlet in the male and in these the rectum was cut off just above the anus and the stump was closed. In all of these,

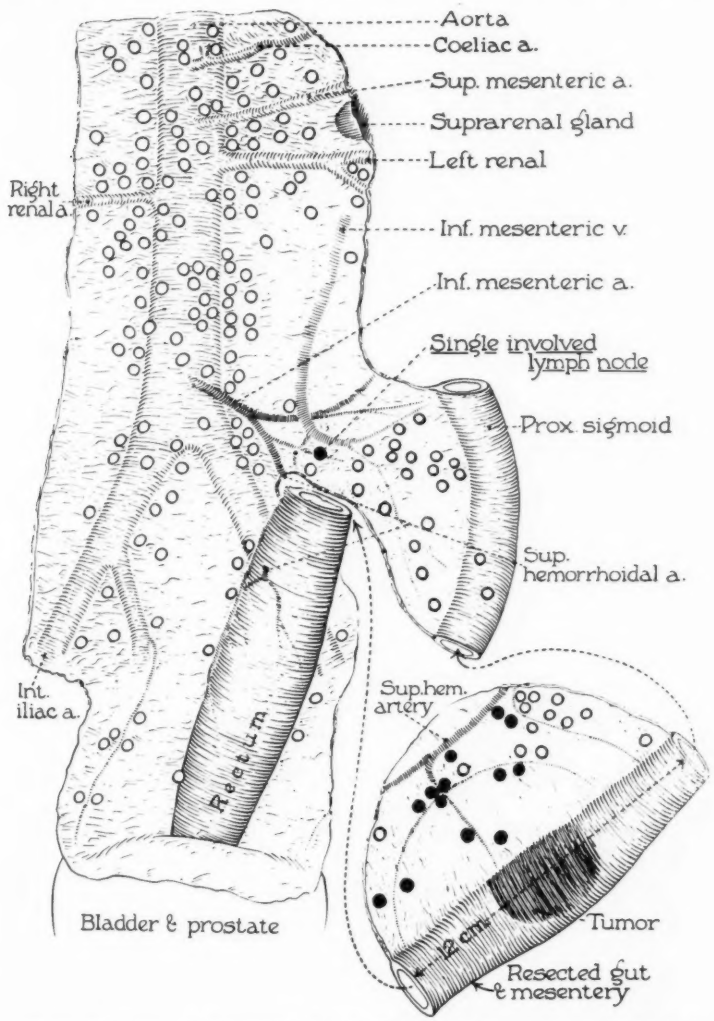

Fig. 9. No. 37719. A 66 year old fat man. He had had a known coronary thrombosis 10 months before. The lesion was 1 inch above the peritoneal reflection. It was the size of a fist and there was a mass of nodes extending to the promontory of the sacrum. A David type of obstruction resection was performed. He died 14 days after surgery of myocardial failure. One hundred sixty-eight nodes were found in the postmortem preparation. The one involved node was less than 1 cm. beyond the line of resection.

there was an average of 55.3 nodes per specimen sectioned and studied microscopically. One specimen contained 210 nodes, and 6 had 112 or more nodes each. Those having an obstruction resection of the sigmoid or intraperitoneal rectum averaged 41.6 nodes per specimen and one specimen contained 102 nodes. Specimens from obstruction resection of the left colon averaged 40 nodes each and one had 69 nodes. Specimens of the right colon obtained by resection and primary ileotransverse colon anastomosis averaged 54 nodes

TABLE X.—35 CARCINOMAS REQUIRING RESECTION OF ALL OR PART OF OTHER STRUCTURES

	No. patients	Well 5–10 yrs.	Postoperative deaths	Recurrence			No follow-up
				Local	Liver	General	
Presacral fascia	8	3	2	3			
Abdominal wall	4	3			1		
Ureter and bladder	9	2	3	1	2		1
Vagina	6	3	1		1	1	
Urethra and prostate	3	1		2			
Uterus	3		1	1	1		
Bowel	2	2					
	35	14	7	7	5	1	1

each with one having 115. Seventy-two of the 125 specimens having metastases to lymph nodes had 4 or less nodes involved per specimen.

In low lying carcinomas of the rectum, small high lying lymph nodes not uncommonly are found to contain metastases. Specimen No. 36682 is typical of such cases and serves to re-emphasize the fact that the widest possible resection of the mesentery is needed to give a chance of permanent cure (Fig. 5).

Four or less involved nodes in 72 of 125 with involved nodes (Table XII).

Three patients were pregnant when the carcinoma of the rectum was discovered. Two have long time cures (Table XIII).

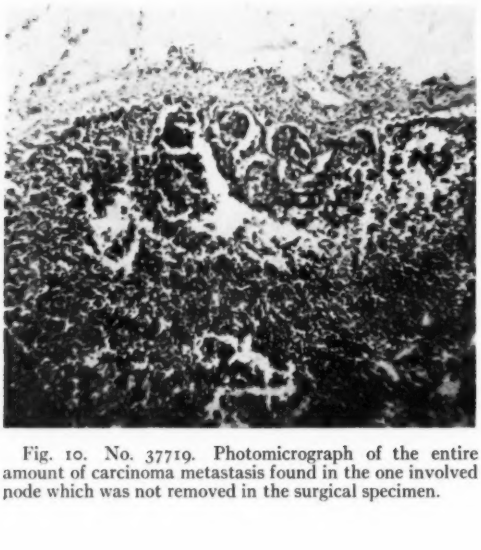

Fig. 10. No. 37719. Photomicrograph of the entire amount of carcinoma metastasis found in the one involved node which was not removed in the surgical specimen.

The first and third patients had full term deliveries 1 or 2 months before surgery. The second patient had an abortion at 4 months.

New carcinomas have developed in 7 of the 200 patients. In each of these cases there is very strong evidence to suggest that these are new tumors and not metastases (Table XIV).

The patient with a previous resection, either with or without a colostomy, must be watched carefully or these new tumors may cause almost complete obstruction before they are discovered.

When there is a double blood supply to the region of the tumor, there is usually a double lymph drainage. We have a number of instances of carcinoma at, or just below, the peritoneal reflection in which we have found metastases to small nodes about 2.5 centimeters lateral to the bowel wall, along the superior surface of the levator ani muscles. Also, either squamous cell carcinoma or adenocarcinoma involving both the mucosa and the perianal

TABLE XI.—RETROGRADE METASTASES TO LYMPH NODES IN CARCINOMA BELOW SACRAL PROMONTORY

	Distance below tumor—cm.
2 with involved nodes	3.5 to 5
2 with involved nodes	2.5 to 3.5
3 with involved nodes	1.0 to 2.5

TABLE XII.—NODES INVOLVED

Operation	Average number nodes	Most nodes per specimen
Miles	55.3	210
Obstruction resection—		
sigmoid and rectum	41.6	102
left colon	40.2	69
right colon	54.0	115

TABLE XIII.—PROGNOSIS IN PREGNANCY WITH CANCER OF THE RECTUM

Case	Age	Per cent Circulation Bowel	Location	Duration symptoms	Operation	Died	Well
1	28	65	Intra-peritoneal	6 mos.	Obstruction resection	2 yrs.	
2	34	75	Extra-peritoneal	6 mos.	Miles		9 yrs.
3	38	80	Extra-peritoneal	4 mos.	Miles		7 yrs.

TABLE XIV.—NEW TUMORS (EXCLUSIVE OF SKIN)

	Nodes at operation	Polyps	Location of new tumor	Died	Well
1. Extraperitoneal	+	o	Transverse colon 7 yr.		9 yrs.
2. Transverse colon	+	o	Rectum 3 yrs. Descending colon 4 yrs.	5½ yrs.	
3. Intraperitoneal	o	o	Splenic flexure 5½ yrs.		5 yrs.
4. Intraperitoneal	o	+	Descending colon 4½ yrs.	4 yrs. 10 mos.	
5. Left colon	+	+	Cecum 7 yrs.	8 yrs.	5 yrs.
6. Left colon	+	+	Breast 4 yrs.	4½ yrs.	
7. Intraperitoneal	+	o	Common duct 2 yrs.	3 yrs.	

skin may have metastases upward to nodes along the superior hemorrhoidal artery as well as to the inguinal nodes. In some cases both groups have been involved. This must be considered when planning surgery.

If we exclude those patients who have died of other causes without any sign of recurrent carcinoma and those who had no follow-up and those who died postoperatively, the prognosis would be as shown in Table XV.

The most striking finding here is in those tumors of the transverse colon, splenic flexure, and descending colon where nodes were involved. All of these had obstruction resections and only 3 of the 8 (37.5 per cent) were alive 5 years. The widest possible resection is indicated here rather than the usual V-shaped wedge of mesentery resected. The favorable prognosis (77.7 per cent) seen in right colon lesions having involved nodes is undoubtedly due to the wide resection of mesentery (54 nodes per specimen) performed when doing an ileotransverse colon resection and anastomosis.

Nineteen died in the hospital after surgery. Eight had no postmortem examinations. Three had postmortem examinations and the usual search was made for metastases to retroperitoneal nodes but none were found; although, all three had had lymph node metastases in the surgical specimens.

In the remaining 8, all of the retroperitoneal tissues from the celiac axis (Fig. 6, No. 41772) to the base of the bladder and prostate were cleared and 96 to 168 lymph nodes (Fig. 7, No. 36303) were examined in each. Two who had no nodes involved in the surgical specimen were free of metastases in the cleared

TABLE XV.—166 CASES OF CARCINOMA OF THE COLON

	Number	Alive 5 yrs.—Per cent
114 alive 5 years	114	68.7
Of 89 extraperitoneal rectal	58	65.2
Of 48 intraperitoneal rectal	36	75.0
Of 11 right colon	9	82.8
Of 18 left colon	11	61.1
Of 100 with involved nodes	54	54.0
Of 66 without involved nodes	60	90.9
Of 53 extraperitoneal with involved nodes	26	49.1
Of 36 extraperitoneal without involved nodes	32	88.8
Of 30 intraperitoneal with involved nodes	18	60.0
Of 18 intraperitoneal without involved nodes	18	100.0
Of 9 right colon with involved nodes	7	77.7
Of 2 right colon without involved nodes	2	100.0
Of 8 left colon with involved nodes	3	37.5
Of 10 left colon without involved nodes	8	80.0

postmortem preparation (Fig. 8, No. 36642). Four who had metastases in the surgical specimen also had metastases in the cleared specimen. In 3 of these 4 (Fig. 9, No. 37719), the involved nodes remaining after surgery could have been removed if the resection had been 1.5 centimeters wider! In one, a resection of all of the inferior mesenteric artery would have been needed to remove all involved nodes (Fig. 10, No. 37719-139). These findings re-emphasize the fact that we must not limit the resection of lymph node containing tissue in carcinoma if we strive for permanent cure.

CONCLUSIONS

1. In this study of 200 patients having resection for carcinoma of the colon, there was a 96.5 per cent 5 year follow-up. One hundred and fourteen were known to be alive 5 to 10 years (57 per cent). In the study of the surgically removed specimens, microscopic sections were made of over 10,000 different lymph nodes, carefully plotted as to location to tumor and surgical landmarks. A number of facts stand out.

2. There is a real need for uniform and accurate description of the location of the tumor when discussing the value of different operative procedures in carcinoma of the colon and rectum. We have suggested an easy and accurate method for locating those tumors below the promontory of the sacrum.

3. Cases of palliative resections where known metastases are left in the liver, lung, etc., should not be included in discussions of surgery for cure of carcinoma, since the inclusion of such cases tends to confuse the reader.

4. The 37.5 per cent 5 year survival rate of those having carcinoma of the left side of the colon when lymph node metastases were present indicates the need for the widest possible resection of mesentery rather than the usual V-shaped wedge of mesentery resected in these cases. The favorable prognosis seen in right colon lesions having involved nodes is undoubtedly due to the wide resection of mesentery (54 nodes per specimen) performed when doing an ileotransverse colon resection and anastomosis.

5. Retrograde metastases to nodes 1 to 5 centimeters below the tumor occurred in 7 of the 153 tumors below the promontory of the sacrum (4.6 per cent).

6. New carcinomas developed in 7 patients who had had resections. This does not include carcinoma of the skin. In some, the diagnosis was not made for several months after symptoms appeared. Patients who have had one cancer of the colon should be re-examined carefully whenever any symptoms suggesting carcinoma appear.

7. In evaluating the type of procedure used in treating carcinoma, the survival rate is important. Of those who died of recurrence in less than 5 years, two-thirds occurred within 3 years and one-third between 3 and 5 years. Six of those listed as 5 year cures developed recurrences and were dead or dying in less than 7 years. In view of the appreciable percentage who develop recurrence in the fourth and fifth year after operation, it seems unwise to consider anything less than a 5 year survival as a cure. Such short term survivals should not be included in discussions since they lead the general practitioner to false conclusions.

8. In carcinoma at and below the peritoneal reflection where lymph node metastases were present in the surgical specimens, 23.2 per cent developed local recurrences and 15.9 per cent developed liver recurrences within 5 years.

9. Postmortem examination of those dying in the hospital after resection for carcinoma of the rectum showed that the ordinary postmortem examination will usually fail to demonstrate small metastases in the remaining retroperitoneal lymph nodes. Four of 11 who had postmortem examinations were found to have metastases to nodes in the retroperitoneal tissues. In 3 of these, complete removal of all node metastases would have been obtained if the field of resection had been 1.5 centimeters wider. It is interesting to speculate on the fate of the cancer cells left in these nodes had the patient lived. In some, inflammation might have resulted either in death of the cells or fixation in heavy fibrous tissue. It is not unlikely that such metastases in lymph nodes missed at operation finally grow. They might grow to great size without giving symptoms.

We have sections of the blood vessels supplying involved lymph nodes being invaded by cancer. Possibly emboli from such a source might be responsible for the sudden appearance of multiple metastases many years after resection of the primary growth.

Finally, this study indicates the need for the widest possible resection in carcinoma of the colon. Lesions which are partially or completely below the peritoneal reflection have a high incidence of local and liver recurrence. The Miles operation seems to give the best chance of cure here.

As far as lesions within the peritoneal cavity are concerned, we have performed obstruction resections on several in this series that could be palpated when doing a rectal examination. This is *justified if not only the bowel wall* but the *blood vessels and lymph bearing tissue* are resected at least 1½ to 2 inches below the lesion as well as to a point just distal to the first sigmoid artery; this is a point about 1½ to 2 inches *above* the promontory of the sacrum. If such resection is not done, involved nodes will be missed. The David extraperitoneal procedure will allow for such a resection in many. If, after such an extensive resection of mesentery there is still an adequate blood supply to the distal loop, we do not object to an end-to-end anastomosis. The real question in the discussion about end-to-end anastomosis is missed, it seems to us. It should be "Can you remove all of the cancer?" and not, "Can you sew two ends of bowel together?" Obviously, in those intraperitoneal lesions below the promontory of the sacrum which are large or have palpably enlarged nodes, the abdominoperineal resection will give a greater chance of cure.

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EDITORIALS

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ESOPHAGITIS

IN recent years much has been written concerning diseases of the esophagus. Carcinomas of the esophagus are found rather commonly and thoracic surgeons are performing resections of the esophagus for this condition with increasing frequency. Many articles are appearing in the literature concerning the therapy of cardiospasm, congenital anomalies, cicatricial strictures, diverticula and benign tumors of the esophagus. Such topics as functional dysphagia, the Plummer-Vinson syndrome, esophageal perforations, foreign bodies, and esophageal varices have received their share of consideration.

Although the aforementioned conditions have been discussed rather widely, esophagitis is a subject that has not received the attention it deserves in medical literature. A number of years ago Vinson and Butt[1] stated that esophagitis occurs more frequently than does any other condition which affects the esophagus. In the course of some 3,000 necropsies they found evidence of esophagitis in 7 per cent of the cases. Yet in the review of the records of these patients they found that symptoms of esophagitis were recorded in only 10 per cent of the group of patients who subsequently were found to have inflammation and ulceration of the esophagus. Apparently esophagitis is a condition which is seldom recognized during a patient's life. Paul[2] has stated that acute ulcerative esophagitis is a common finding at necropsy but rare in clinical practice.

Esophagitis is a condition that should be of great interest to the surgeon. It usually occurs in patients who have diseases which require surgical treatment or in patients who have undergone major surgical operations. Vinson and Butt found that in 75 per cent of their 213 cases of esophagitis the patients had been operated upon a short time before. The disease is encountered most commonly in patients who have gall-bladder disease, duodenal ulcer,[3] obstructing lesions of the gastrointestinal tract and esophageal hiatal hernias. Selye[4] was able to produce hemorrhagic esophagitis by ligating the pylorus in experimental animals. In some instances, esophagitis appears to follow severe infections of the upper part of the respiratory tract.

Why does esophagitis occur? Certainly a number of factors are involved and deserve consideration. The trauma caused by the passage of nasal tubes may predispose to esophagitis. Certain abdominal conditions and operative procedures require that such

[1]Vinson, P. P., and Butt, H. R. J. Am. M. Ass., 1936,106: 994-996.

[2]Paul, L. W. Radiology, 1943, 41: 421-430.
[3]Benedict, E. B., and Daland, E. M. New England J. M., 1938, 218: 599-601.
[4]Selye, Hans. Canad. M. Ass. J., 1938, 39: 447-448.

tubes remain in place for a considerable period of time. However, I doubt very much that introduction of nasal tubes alone is often responsible for serious esophagitis, although in the presence of pre-existing esophagitis it may do a great deal of harm.

Attention should be called to the occasional occurrence of perichondritis and stenosis of the larynx as a result of use of a nasal tube in the esophagus. Strictures in the vicinity of the cricoid cartilage are particularly susceptible to the pressure effects of such tubes. Although the use of nasal tubes is a valuable adjunct to the therapy of some abdominal diseases, these tubes should be used with discretion and for as short a time as is possible.

More commonly esophagitis is caused by the reflux of gastric secretions into the esophagus. These digestive juices are very irritating to the esophageal mucosa. Esophagitis is likely to occur in association with abdominal diseases that produce excessive vomiting. Incompetence of the cardiac sphincter likewise results in regurgitation of gastric acids into the esophagus. The cardiac sphincter is incompetent in many cases of esophageal hiatal hernia and esophagitis frequently is associated with hiatal hernia. Years ago Harvey Cushing[1] called attention to the frequent occurrence of esophagitis and esophageal ulceration in patients with lesions of the brain. Pathologists often describe ulcers of the esophagus in cases in which death was due to brain tumor.

The symptoms of esophagitis frequently are overlooked. Such terms as "heartburn" and "sour stomach" often are used by patients to describe a substernal and epigastric burning sensation caused by inflammation of the lower part of the esophagus. In cases in which the disease is severe patients may complain of substernal pain, sometimes referred up to the throat and neck and even into the arms. Such pain usually indicates esophageal spasm, and some of the cases fall into the category described by Moersch and Camp[2] as diffuse spasm of the esophagus. In such cases severe dysphagia may develop. Of interest is the work of Dey and his associates[3] who demonstrated that reflex spasm and shortening of the esophagus may be produced in experimental animals by stimulation of the vagus nerves, by manipulation of the stomach, liver, and other abdominal viscera, and by distention of the gall bladder.

In cases of severe ulcerative esophagitis, hemorrhage may occur. In their series of cases in which necropsy was carried out, Vinson and Butt found that 32 of 213 patients had presented symptoms of esophagitis. Of these 32 patients 53 per cent had complained of substernal burning, 40.8 per cent had had hematemesis, and 28 per cent had complained of difficulty in swallowing. In view of the fact that in all of Vinson and Butt's cases necropsy was performed, they are not representative of the usual cases seen clinically. The majority of patients who have undergone operation will not describe symptoms of esophagitis unless careful inquiry is made.

In most cases esophagitis probably subsides without leaving any ill effects. However, repeated episodes of esophagitis lead to a progressive cicatrization of the lower part of the esophagus. Recently, Harrington and I[4] have shown that an actual shortening of the esophagus may occur with stricture at the esophagogastric junction. Repeated episodes of ulcerative esophagitis and healing of the esophagus are usually responsible for the short esophagus type of esophageal hiatal hernia. This condition most commonly occurs in association

[1]Cushing, Harvey. Surg. Gyn. Obst., 1932, 55: 1-34.

[2]Moersch, H. J., and Camp, J. D. Ann. Otol. Rhinol., 1934, 43: 1165-1173.

[3]Dey, F. L., Gilbert, N. C., Trump, Ruth, and Roskelley, R. C. J. Lab. Clin. M., 1946, 31: 499-506.

[4]Olsen, A. M., and Harrington, S. W. Unpublished data.

with duodenal ulcer, gall-bladder disease and other abdominal diseases which produce regurgitation of gastric secretions. Esophagitis and shortening of the esophagus may develop in cases of hiatal hernia because of reflux of gastric acids into the esophagus. In cases of short esophagus with intrathoracic stomach, usually the shortness is not congenital. Shortening is caused by recurring ulcerative esophagitis and is frequently secondary to surgical lesions of the abdomen. The conclusions reached by Harrington and me were similar to those reached by Allison[1] and by Smithers.[2]

The fact that esophagitis is not an uncommon complication of disease of the upper part of the abdomen must be recognized. When surgical intervention is indicated it should not be delayed. Gastric secretions should be neutralized with antacid preparations in cases in which these secretions are regurgitated into the esophagus. At times elevation of the head of the patient's bed is helpful in preventing a reflux of gastric acids. In the postoperative period inquiry should be made concerning symptoms suggestive of esophagitis. Nasal feeding tubes should be used with some discretion when the presence of esophagitis is suspected. Sometimes esophagoscopy is indicated. If cicatrization and stricture occur, relief of dysphagia usually can be obtained by dilatation performed over a previously swallowed thread. ARTHUR M. OLSEN.

PREPUBERTAL MELANOMA OF SKIN

THE groups of neval cells constituting this congenital tumor may be in visible evidence at birth, particularly in the very large lesions, such as the bathing trunk nevi, or those which occupy a wide expanse of skin. The coloration of these tumors, however, seems to proceed after birth with exposure to light; in other words, the elaboration of the pigment does not seem to occur greatly *in utero*. By the time the child is a few years old, these tumors become much darker in color. Many of them do not increase in dimension except proportionately with the rate of the growth of the child. It is evident in studying the phenomena of the development of pigmented nevi that many of these nevi are not at all visible until after the onset of puberty. A child with a few scattered pigmented moles here and there may, in company with the endocrine changes attendant on the state of puberty, have the rather sudden development of numerous pigmented nevi over the skin of the face, trunk and extremities. It is assumed that these are not new-growths, in the strict sense of the word, but that the congenital misplacement of these cells may have been present but unrecognized until influenced by the hormonal factors so increased at this time. The nevi also undergo some remarkable pigmentary changes with the onset of puberty in that they become much more darkly pigmented and have a tendency to become elevated above the level of the surrounding skin.

There is one important type of pigmented nevus which bears such a close resemblance to malignant melanoma that it is not possible, clinically, to distinguish between the two. This nevus may be found in children from ages of one to the time of puberty. Usually they are rather darkly pigmented, bluish, blue, black, or dark brown in color, smooth and well demarcated. When this tumor is excised in infancy or childhood and submitted to pathologists for diagnosis, they are frequently unable to state whether the neoplasm is benign or malignant, inasmuch as the histological criteria, exclusive of invasion and permeation of vessels, are practically identical with the malignant variety of melanoma as encoun-

[1]Allison, P. R. J. Thorac. Surg., 1946, 15: 308-317.
[2]Smithers, D. W. Brit. J. Radiol., 1945, 18: 199-209.

tered in adults. Even though the tumor has structurally the conformation of the true melanoma, it ordinarily does not behave as such until after puberty. Our experience with now more than nine hundred cases of malignant melanoma has been that none of these melanotic tumors of infancy and childhood has metastasized to regional lymph nodes, although many of them have been labeled as malignant melanoma by extremely competent pathologists. This fact is now so well recognized that our pathologists insist on having clinical information available concerning the age of the individual and whether or not evidences of approaching puberty exist. For example, a diagnosis of "juvenile cellular nevus" may be made on a tumor excised from an adolescent boy only to discover some months later that inguinal lymph nodes contain metastatic melanoma: the youth showed evidences of pubertal changes. We might well adopt such a term as *prepubertal melanoma* to indicate the group of tumors which resemble malignant melanoma histologically but do not behave as such.

It is our belief, therefore, that the malignant melanoma in its derivation from the pigmented nevus, is a tumor closely related to the endocrine system and markedly influenced by the activity of the endocrines, notably the gonads, the suprarenal cortex, and the hypophysis. In keeping with this opinion, we have often observed malignant melanomas to occur in adolescent girls and boys just after the age of puberty, and furthermore, we have commented on the extremely rapid growth and wide dissemination of these tumors at this early age. Apropos of these statements concerning the stimulation of the tumor by hormones, it may be mentioned that we have never seen a patient who developed a malignant melanoma during pregnancy, survive for any length of time. We have had quite a number of instances in which a pigmented nevus underwent malignant degeneration into melanoma during pregnancy or shortly thereafter, and when this occurred, the tumor grew with startling rapidity and was usually widely disseminated without control by surgical excision, however radical, or by any other methods of treatment.

The significant conclusion to be drawn from these observations is the obvious necessity for complete surgical removal of all dark, deeply pigmented nevi in childhood. Their removal in infancy and childhood entails very minor surgical procedures without the hazards of recurrence. It may be a serious mistake to delay this operation until some evident change has occurred in the appearance of the tumor, sufficient to cause worry, particularly if this change develops at the time of, or shortly after, puberty. In reviewing the end-results of the treatment of melanoma at the Memorial Hospital, the number of 5 year survivals without recurrence (definitive cures) was only 50 per cent as good in the group of patients whose ages extended from puberty to 25 years as it was in the older age group. A microscopic diagnosis of melanoma in a skin tumor removed during infancy and childhood does not call for an extension of radical surgery such as wide excision and skin grafting and dissection of regional lymph nodes, provided the child has not entered the pubertal stage. This last statement is based solely on our personal experience at the Memorial Hospital in a series of more than 900 malignant melanomas. When we investigated the rumored instances of metastasizing prepubertal melanoma from other hospital sources, we encountered only one instance in which the sectioned lymph node contained apparent melanoma cells; in the other instances the tumors were bizarre and of uncertain histogenesis.

GEORGE T. PACK.

From *The History of England* by David Hume. London: Cadell, 1796.

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BELLS TOLL FOR PRIMES

An Inquiry into the Fate of William the Conqueror

FRANCES TOMLINSON GARDNER, San Francisco, California

THE deathbeds of personages of historical importance are pried into with the enthusiastic curiosity of small boys turning over a dead lizard. Human nature enjoys meditation on the fact that the last mortal moments of the great are very similar to and no more comfortable than those of the common herd. It is pleasing to learn that the mighty of the past, though surrounded by voluminous soiled velvet and many dented golden vessels, still writhed on the same old bed of pain.

So, William the Conqueror met death. Praying, declaiming and groaning, he departed this life on the 9th of September, 1087, in the depths of the Middle Ages when medical observation was at its lowest ebb and his devoted attendants so consumed by their eagle-eyed watch for the devil or any hovering angels that their interest amounted to espionage. They remembered every word of his remarkable deathbed discourse and were admiringly attentive to the manner in which his departing spirit met its Maker, but all they knew about his illness was that he was very stout, had gotten very hot and tired, and had bumped into the pommel of his saddle. They gave never a thought to what, in William's life, food, habits, and manner of living, bore upon his painful end, or, what mechanics of the body caused that end.

He was born in the last month of 1027 or a very early month in 1028 to Robert, Duke of Normandy and his mistress, Harleve, also called Arlette, the beautiful daughter of the local tanner. His father, somewhat vividly known as Robert the Devil, died at the age of 35 in the traditional best manner, while on a pilgrimage to the Holy Land. His mother, taking his little sister Adeliz by the hand, soon went off to marry Herlewin of Conteville, by whom she bore two half brothers for William and Adeliz. These were trying and turbulent Odo, later Bishop of Bayeux and Earl of Kent, and Robert, Count of Mortain, just a normal unimpressive relative.

In his youth and middle age William was stocky but well proportioned with a neck somewhat longer than the average and shoulders so wide and powerful that even in his waning years he could pull, while seated on his horse, a long bow too heavy for his archers standing on the good firm earth. His life was one spent in fighting, brawling, and battle, but in spite of all to which his body was subjected no mention is made of any wound or debility until he was a man in his fifties, a comparatively ancient age for the eleventh century. He was, by nature, an aggressive extrovert. He was ruthless, brutal, stern, frightening, kind, gay, and loving, all to an extreme degree. In the interests of his position in life he cultivated an expression of ferocity which went well with his high bald forehead and which frightened away much weak-hearted opposition.

Dietetically he was seasonal, which was forced upon him and all his fellows by the ignorance of the times. In the good months of the year he ate his beef, boar, venison, and mutton for breakfast, lunch, and dinner. Since his kitchen contained nothing that would approximate a modern stove his meat was roasted on a spit turned by a half-hearted kitchen boy and served red and dripping. Consequently though not very hygienic and frequently full of parasites, it presented his inner economy with all its available vitamins. He partook occasionally of chicken, and, very reluctantly, on fast-days, of fish. He refused to have much to do with the few vegetables of the time, frowning on them as women's fare, but he could be coerced into real enjoyment of a "mortreuse," a meat and vegetable stew, provided it was fancily dressed and accompanied by plenty of rich sweet

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liquor, usually mead. His flour, made up into large round loaves or served as his favorite dessert, bag pudding, a kind of forerunner of modern apple pudding, was roughly ground and often unbolted and retained all its useful vitamins. His garden supplied him with wizened but succulent little plums, apples, and pears for a finish for his gigantic trencherings.

The picture was very different in the winter. All the meat was crudely dried, salted, or pickled. There were few, if any, vegetables. The fruit was gone and the flour was damp and moldy. William ate so badly that he, like all his people, met the return of spring with his annual touch of scurvy, as commonplace in those days as spring fever. William ate of the fat of the land, but in cold winter the land was, indeed, not very fat.

William may have had trouble with constipation brought about by a combination of such things as diet, winter restrictions on his customary exercise, and the lack of reasonable hygienic arrangements about his castle. I do not mean to infer that anyone of the period was squeamishly modest, but icy cold castles can force a certain added reluctance on a sluggish colon. William may have built up a strong tendency to a condition which, as his years grew longer, could well have become chronic.

Somewhere between his fiftieth and his fifty-ninth year serious changes took place within the previously impervious body. He grew corpulent out of all proportion to his build and in 1086, when he was about 58, was forced to take to his bed, in Rouen, under care of what physicians were available, for the reduction of his "corpulence." This obesity seems to have been genuine fat, honestly come by, since nowhere is there mention of tapping or of water logged tissues. Had there been, there would have been comment, because if there was any condition an eleventh century doctor could recognize it was the presence of edema. By the process of eliminating other things excluded by William's physique and activities and the silence of his contemporaries we can omit ulcer, cancer, hernia, heart and kidney disease. However, it is not in the character of such a man to lie meekly in an uncomfortable bed for several weeks when enemies all around him might take advantage of his impotence so that something greater than simple adiposity forced him to give up.

It is a fair guess that William was suffering from diverticulitis of the colon. It would be impudent of an author writing today, using the little information which is available, to declare just where the diverticula might be or whether there were many of them. Perhaps it is presumptuous even to suppose that he had them, but his age, his vague distress, his grossly fat body, and his probable chronic constipation clamor their acceptance of the condition. A long history of epigastric discomfort which evidently also had long periods of remission and comparative comfort, coupled with no history of anything startling in addition, points to a comparatively asymptomatic diverticulosis which, gradually becoming more and more unmanageable, finally put William to bed. It is a predicament which, in its subtle obscurity would unquestionably baffle an eleventh century physician whose treatment could consist of little more than emetics, purges, and bed-rest.

While he was reposing at Rouen his cousin Philip, King of France, found time to be caustic about him. In public, Philip remarked that he was surprised that his Brother England should be so long a time in being delivered of his big belly. This uncouth insult was promptly conveyed back to the sick room where its effect was volcanic. William was not devoted to Philip at any time and had a little bone to pick with him in the matter of the Vexin, a province once his own which, through many involved negotiations between vassals and overlords, had been annexed by Philip. For 10 years William had been too busy to get it back again but now he seized upon the old quarrel as a pretext to retaliate for Philip's spiteful comment which William interpreted as likening him to a woman lying-in. He rose from his bed with a roar exclaiming that, at his churching, he would set all France ablaze. This cryptic statement referred to the custom of a woman carrying a candle to her churching after childbed. William would allow no one, least of all the King of France, to suggest that he was womanish.

The last week of July 1087 he appeared suddenly before Mantes which be besieged and, on the 10th of August, took. On entering, his orders to his troops were "scatter, pillage, and burn," which they obeyed to the letter. They removed everything movable and burned everything inflammable, including the churches and the standing corn. The huge, sick, old man rode everywhere, shouting and scowling. The summer heat was torrid and the flames from the burning buildings added nothing to the comfort of man or beast. William's horse, weary from the enormous weight of its rider, heavier than ever because of his armor, excited by the flames and guided by a careless hand, stepped upon a burning ember. It was said solemnly, at the time, that God caused this to happen as punishment for the terror visited upon the town. Doubtless William deserved the punishment but it is more likely that God was occu-

pied elsewhere and that the flaccid old body, taken by surprise, could not counter the startled leap of the charger. He was flung against the high hard pommel of his saddle and something serious happened within him.

He was carried back, by litter, to Rouen. Physicians arrived in the persons of Gilbert Maminot, Bishop of Lisieux, and Goutard, Abbot of Jumièges "with some others well skilled in medicine." These learned and holy counsellors hovered around his bed during all the few weeks which remained of his life, hung adoringly on each word of his noble and long-winded confession and oration which filled his last days, exorcised his spiritual devils, and seem to have entirely omitted to bother about his physical ones. Word for word of his conversations with his sons, his bequests of his substance, his speeches to the holy family, have been given us but neither Gilbert nor Goutard left so much of a clinical note as "vomited" or "fevered."

He languished at Rouen. The heat was terrible as were the stinks and flies of that medieval city. So were the shouts and cries of peasants and market folk and driven cattle and all the thousand noises of the narrow streets. William asked to be taken to the church of St. Gervase which lay a short way out of the city. His physicians agreed to the brief journey and he was installed in the priory there where breezes blew away some of the heat and the only noise was made by the quiet steps of soft footed monks.

During the 4 weeks of his dying William's mind was as clear as his body was agonized. In his famous deathbed oration which must have continued daily for most of the period of his last illness, he confessed to all his sins and depredations, apologized to those he had wronged and begged the forgiveness of the church for all he had done against it, none of which, of course, had he done intentionally. He called his sons William Rufus and Henry to his side and gave them his bequests in his own voice. Robert, the eldest, was in Germany. William gave him the Norman inheritance with the peevish remark that Robert was a "proud and silly prodigal and will have long to suffer severe misfortune." He did not care for Robert. England went to William Rufus who was admonished to be less a king than a watchful servant of God. William was a little ashamed of the way in which he had acquired England himself and felt that he should make some amends for his behavior. William Rufus was dispatched to England on the day before his father's death to study, under the good Bishop Lanfranc, how to be a good king. What success Lanfranc had in his teaching can be read in the history of Rufus' reign which was of such cruelty and terror as to make William's sins seem lily white.

Henry, the third son, was given only money. This brought a wail from Henry who said that 5,000 pounds was nothing if he could not have a corner of the earth to call his own. Soothing him, his father predicted that this boy would succeed to all the dominions that were William's and would surpass his brothers in power and wealth. William knew his sons. Robert and William Rufus died as shiftlessly as they had lived, but the canny Henry was King of England and Lord of half of France before he finished.

William grew no better. The blow from the saddle, while it did not rupture the distended sac of one or another of his chronic diverticula, evidently caused such injury to the walls that it slowly necrosed. He must have become more and more toxic and the sac more and more inflamed until, during the night of the 8 to 9th of September, it ruptured at last, and peritonitis intervened.

The end came in the early morning of September 9, 1087. William, who, for 4 weeks, had rent the air with groans and torn the bed with writhings, had spent the previous night in quiet undisturbed slumber. As the sun rose he woke to the sound of bells and, in a weak voice, asked what they might be. He had become disoriented for they were the same bells he had heard all the weeks that he lay there, the bells of the Cathedral of St. Mary, in Rouen, routinely tolling for primes. William made one more impassioned well-turned speech commending himself and his soul to God, the Virgin, and Jesus Christ, and with dramatic perfection raised his hands to heaven and drew his last breath with his last well chosen word.[1]

Hardly had his chest stopped heaving than a great metamorphosis overcame the pious atmosphere of the bed chamber. His devoted watchers picked up their voluminous skirts and vanished, all on the same mission. They ran toward their bequests. The body servants stripped the body, searched the room, turned out the bed, and fled, leaving the unlamented Duke lying naked on the floor. Henry, not too indifferent to his 5,000 pounds, was already on his way to where his money was to be found. Not until 3 hours later,

[1]Denique quinto idus Setembris, feria va, jam Phoebe per orbem spargente clara radiorum spicula, excitus rex sonum majoris signi audivit in metropolitana basilica. Percunctante eo quid sonaret, responderunt ministri: "Domini, hora prima jam pulsatur in ecclesia Sanctae Mariae." Nunc rex summa devotione oculos ad coelum erexit, et sursum manibus extensis, dixit: "Dominae meae, sanctae Dei genitrici, Mariae, me commendo, ut ipsa sanctis precibus me reconciliet carissimo filio suo Domino nostro, Jesu Christo." Et his dictis protinus expiravit. *Ordericus Vitalis: Historiae Ecclesiastiae.* Libri tredecim. Paris, 1845 ed.

when the bells rang for tierce, did any one return to pick up the body and carry it away.

The Archbishop of Rouen ordered the remains sent to the Abbey of St. Stephen at Caen for burial because William, having built this church in payment of the dispensation which enabled him to marry his cousin Matilda of Flanders, had a personal sentiment about it. The order having been given it was found to be the embarrassing truth that there was none who would advance the funds for the many expenses of the funeral or take charge of the body for the trip. Henry was unavailable, counting his silver, and William Rufus was in England. Nobody seemed able to locate Robert, somewhere in Germany. Everyone else, including William's reverend but stormy half-brother, Odo, Bishop of Bayeux, had evaporated. Finally from nowhere came a dusty, rather frowsty country squire named Herlewin who, from the depths of his shabby armor brought forth sufficient gold to pack up the corpse and convey it to Caen.

It was a long hot journey. Herlewin had time to contemplate the ingratitudes of the beneficiaries of the late Duke. Perhaps he sent an outrider into Caen to stir up some sort of welcome, for, a few miles from the city the meager little procession was met by the Abbot of St. Stephens, by Henry, who had finished counting his silver, and by an assortment of clerks and laymen. Even Odo had bobbed up. The body was conducted to the Abbey with some pomp and laid on a bier while somebody hurriedly began the construction of a sarcophagus.

As the services began commotion was heard outside. Flames were seen bursting from some of the houses of Caen. With one accord Bishops, Prince, clerks, monks, and laymen laid aside their melancholy and ran to fight the fire. William lay alone, except for Herlewin, until the town was safe.

The fire out, Gilbert, Bishop of Evreux, magnificently ascended the pulpit and began his discourse upon the qualities of William the Bastard, Duke of Normandy and Conqueror of England. The story of William's accomplishments and piety was becoming impressive when, as the Bishop paused for breath, a loud voice was heard among the congregation. It belonged to a certain Ascelin Fitz-Arthur who shouted that the land upon which the Abbey of St. Stephens stood belonged by rights to his father, Arthur, from whom William had wrested it by force. Never, said Ascelin, would he allow the body of this man to lie in its stolen soil. In the embarrassed silence which followed the declaration Bishop Gilbert hurriedly came down from his pulpit and Henry as hurriedly moved to meet him. Together they faced the angry Ascelin across the open grave.

After considerable haggling it was found that Ascelin's injured heart responded to the sound of silver. Grudgingly he allowed 60 shillings to be counted into his hand. For this, and the promise of 100 silver pounds, to be delivered at a later date, he graciously allowed the service to go on.

At last the body was taken from the bier to be placed in the stone coffin between the altar and the chancel. Now another dreadful fact was discovered. The coffin was too small. There was nothing to do but force things a little bit. A little bit was just a little too much for the body after all it had been through between St. Gervase and the present moment. The conditions at death, the time element, the inept enbalming, and now this violent compression, conspired to put a final strain on William's weak abdominal wall. It burst.

As the stench filled the church the last shred of dignity left the obsequies, The lid of the coffin was clapped on hurriedly and, once more, people poured from St. Stephens. William lay alone as he would lie until the sacking of the church 500 years later when his bones were disinterred and rudely treated. At that time it was discovered that, at least, he had been given one royal touch. His body was found wrapped in crimson taffeta.

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REVIEWS OF NEW BOOKS

THE book on *Preoperative and Postoperative Care*[1] written by William J. Tourish and Frederick B. Wagner, Jr. presents the routine and methods used by these men in their surgical practices.

It is very well prepared and will be found an invaluable aid to internes and residents. The procedures given are those followed by the authors, but they wisely point out the necessity of being alert for other methods which are equally good, and which when found useful should be accepted. While routines are necessary and useful, their maximum benefit is achieved only when each patient is treated as an individual problem, and such changes made as may be necessary for intelligent application of the routines in each specific instance. It has additional merit in that it gives detailed specific measures of examination and all phases of treatment.

The constant observation and treatment both before and after operation are stressed. In difficult and controversial cases the importance of seeking the opinions and advice from an internist and from specialists in other fields is emphasized.

The first two chapters deal with the general preoperative and postoperative care. Chapter III describes the management of specific groups of surgical problems. Chapter V deals with the care of the urological patient, Chapter VI with the neurosurgical patient, and the final chapter, Chapter VII, which is very well written, deals with the gynecological patient.

This book will serve as a guide to detailed methods and procedures against which the interne or resident may check his own efforts and add those things which are necessary. R. T. BOTHE.

THE monograph *Aspetti di patologia placentare*[2] by Massimo Macciotta presents a very detailed and extremely interesting description of the changes found in the placenta in various diseases of the mother. The diseases considered are the pathological conditions of the kidney due to pregnancy, eclampsia, nephritis, syphilis, tuberculosis, infectious diseases, malaria, intrauterine death of the fetus, and heart diseases.

In addition to the macroscopic findings, such as hypertrophy of the placenta, variations in consistency, color, and weight, and particularly variations in the proportionate weight of fetus and placenta, the microscopic findings are discussed, including the finding of Langhans' cells, regressive and proliferative changes in the vessels, various regressive changes in the stroma, the red and white nodules so frequently seen, and hemorrhagic foci. The article is profusely illustrated with photomicrographs of the findings, and tables are given showing the percentages of the individual findings in the various diseases.

While there are certain findings which are characteristic, such as the destruction of the amniotic epithelium, which is seen almost exclusively in maceration of the fetus, the hypertrophy of the villi and the eccentric endarteritis obliterans of the vessels of the villi, so frequent in syphilis, and the finding of parasites in the red blood cells in 70 per cent of the cases of malaria, there is no picture that is absolutely pathognomonic of any of the diseases in question. But if the different pathological findings are checked with a table of the frequency of their appearance in the different diseases valuable indications as to diagnosis are given. The monograph is worthy of careful study. AUDREY G. MORGAN.

THE second volume in the series of textbooks which is being published under the general heading of *The Rehabilitation of the Injured*[3] has recently appeared. It deals with specific remedial exercises and is not concerned with general exercises, games, and recreational activities, which will be included later in a volume on recreational therapy. Passive therapy has not been included, as its use in the treatment of traumatic conditions has been described fully in many of the standard textbooks on physical medicine

Watson-Jones in his foreword brings out several good points. "The death knell of massage has been sounded. No longer must the patient be lulled to sleep with soothing massage; he must be galvanised into activity by invigorating exercise."

"Rehabilitation of the injured begins with surgical and manipulative treatment, which is accompanied and followed by physiotherapy, exercise therapy, occupational therapy, and recreational therapy, and is completed by retraining and resettlement. The process is involved and prolonged. But two principles may be recognised. The first was known to Galen hundreds of years ago: Confidence and hope do more good than physic; he cures most in whom most are confident. The patient must be encouraged; he must be stimulated; he must be inspired; he must learn that success depends upon his effort alone. But the second principle is equally important. Rehabilitation calls not only for recreation; it calls for work and very hard work."

[1] PREOPERATIVE, AND POSTOPERATIVE CARE. By William J. Tourish, M.D., F.A.C.S., and Frederick B. Wagner, Jr., M.D. Foreword by Thomas A. Shallow, M.D. Philadelphia: F. A. Davis Co., 1947.

[2] ASPETTI DI PATOLOGIA PLACENTARE. (Pathology of the placenta.) By Massimo Macciotta. Bologna: Nicola Zanichelli, Editor, 1947.

[3] THE REHABILITATION OF THE INJURED. Vol. 2: Remedial Gymnastics. By John H. C. Colson. Foreword by Sir Reginald Watson-Jones, B.Sc., M.Ch., Orth., F.R.C.S. London: Cassell & Co., Ltd., 1947.

The literature of rehabilitation is of two kinds: generalizations and the much more rare utterances of those who know how to do the job and who have the gift of imparting the knowledge to others. The author, Mr. Colson, is among the latter. This book cannot fail to interest medical men, particularly surgeons and physical medicine specialists. It will be of particular value to physiotherapists whose work is to apply and elaborate the principles underlying exercise therapy. JOHN S. COULTER.

THE recent book by Hans May has been called quite appropriately *Reconstructive and Reparative Surgery*[1], since it emphasizes the correction of anatomic defects in all fields of surgery. The basic concept of the book, whether dealing with general principles, with anatomic regions, or with specific problems of repair is that there are but a few fundamentals underlying all surgery. These fundamentals do not change with the particular field of the individual surgeon but are the same whether dealing with the head and neck, the trunk, or the extremities. One is not surprised therefore to find described operative procedures for repair of nonunion of the long bones next to discussion of arterial repair and obliterative aneurysms. Nor should the surgeon be startled to find in what is ostensibly a book on plastic surgery discussion of the repair of incisional abdominal hernia, and anal sphincter defects alongside excellent descriptions of correction of lip and nasal defects, deformities of the ears, eyelids, and orbits.

Barrett Brown in his introduction to the volume states that "actual procedures are relatively few and they may be carried from field to field." Actually the principles of plastic surgery are the principles of good surgery whether we deal with general surgery or orthopedics or ophthalmology. To many surgeons it has seemed that the application to surgery in general of certain principles so essential to good results in plastic surgery has been one of the factors which has made for real advancement in the science. It is therefore quite fitting that this book embraces so many of the surgical specialties.

The volume falls into three major parts although the author has made five divisions. The first part deals with the general principles of reconstructive surgery starting with a discussion of preparation of the patient, instrumentarium, and the various procedures and techniques common to all types of plastic surgery, and includes chapters on wound healing and the treatment of wounds and burns. The second part of the book, divided into three divisions by Dr. May, covers the plastic and reparative surgery of the various anatomic areas—head and neck, the trunk, and the extremities. The third part of the book is devoted to illustrated reports of 125 cases, each carefully chosen to bring out some particular operative procedure or problem.

The volume is most generously illustrated throughout the text by many drawings, photographs, and diagrams of operative procedures. In looking at these excellent illustrations and photographs and on reading the text pertaining to them one realizes that they represent the actual experience and carefully considered judgment of the author.

The book contains much of interest to every surgeon; its range of practical applicability is wide and it should be a welcome addition to that section of the surgeon's library where the volumes are well thumbed, since often consulted. MICHAEL L. MASON.

IN nine hundred odd pages, accompanied by 645 illustrations, the author of *Surgery of the Ambulatory Patient*[2] has completely covered the subject including much material on the diagnosis of conditions requiring hospital care. Despite the fact that the division of surgery arbitrarily into ambulatory and hospital practice is an artificial one, this volume fills a need for an authoritative reference on minor procedures. The decision as to whether a surgeon may treat a patient with a given lesion in a hospital or an office will usually depend on the facilities available locally and thus must be made by each surgeon individually. Many of the patients described in this volume are ordinarily considered as hospital cases by surgeons who have sufficient hospital facilities available.

A comparison of this volume with the first edition shows that the sections on infection have been rewritten to include the use of penicillin which was not available at the time the first edition was published. The section on second degree burns has been completely rewritten, the author now advising nonadherent pressure dressings in the treatment. A new section on the truss treatment of inguinal hernia has been added. Considerable new material has been added to the chapter on the back, including a consideration of the herniation of the nucleus pulposus. The treatment of gonorrhea has been rewritten to include the use of penicillin. A new section has been added on tendon suture as well as new illustrations for this section. In addition to the specific items mentioned a large number of new references have been added to the previous volume. Some new illustrations have replaced older ones. Enough old material was deleted to prevent any increase in size of the book. A table of contents and an adequately revised index are included. THOMAS C. DOUGLASS.

A very comprehensive, carefully compiled treatise *Trichomonas Vaginalis and Trichomoniasis*[3] by Ray E. Trussell is presented as a foundation for more constructive study of a perplexing clinical problem. Despite the wealth of literature which has accumulated since Donné first described the organism and suggested its clinical importance more than 100 years ago, many features of human trichomoniasis

[1] RECONSTRUCTIVE AND REPARATIVE SURGERY. By Hans May, M.D., F.A.C.S. Philadelphia: F. A. Davis Co., 1947.

[2] SURGERY OF THE AMBULATORY PATIENT. By L. Kraeer Ferguson, A.B., M.D., F.A.C.S. 2d ed. Philadelphia: J. B. Lippincott, 1947.

[3] TRICHOMONAS VAGINALIS AND TRICHOMONIASIS. By Ray E. Trussell, M.D. With an introduction by E. D. Plass, M.D. Springfield, Illinois: Charles C Thomas, 1947.

remain almost as obscure as when Hoehne revived interest in the problem in 1916. As the author states in the preface, "—the time has come to replace the older investigative technic with the modern physiologic aproach." This book provides invaluable reference material for any new approach and, as such, will be welcomed by research workers as well as by gynecologists and urologists who seek a comprehensive, unbiased treatise on the subject.

The work is divided into three parts: Part I, "Trichomonas Vaginalis," deals with the morphological, biological and epidemiological characteristics of the organism. Criteria are given for differentiating trichomonas vaginalis from the morphologically similar but separate species which infect the mouth and the intestinal tract. The taxonomic relationship of trichomonas to other protozoa is explained fully in Appendix A, and the complete parasite-host list of trichomonads (with original reference to each named species) is given in Appendix B. This material will interest the research worker and parasitologist. Part II, "Trichomonas Vaginalis Infections," presents in detail the clinical aspects of the disease in women as well as men. Part III, "Treatment," outlines the methods which have been employed in the treatment of human trichomoniasis and lists alphabetically the more than 150 chemicals utilized in efforts to eradicate the parasite, giving the results reported for each. An imposing list of 1,586 references in the bibliography is proof of the zeal with which the author has undertaken the study. To quote again from the preface: " . . . this volume makes the errors and successes of the past readily available for those who would pursue the problem." HAROLD C. MACK.

IN the words of the authors of *Essentials of Pharmacology*,[1] "This book is intended to serve as an introductory text in pharmacology . . . On the other hand, the general principles of pharmacology have been stressed wherever possible, and efforts have been made to indicate what appear to be the coming trends in the field."

This book is a clear and concise coverage of a very extensive field. It is up to date and mentions most of the drugs developed in recent years. Information is to be found here on such drugs as myanesin, mesantoin, tridione, amidone, dibenamine, diisopropyl fluorophosphate, antergan, neoantergan, diphenhydramine, tripelennamine, pteroyl glutamic acid, the nitrogen mustards, British antilewisite, chloroquine, paludrine and pentaquine. In addition, some of the older drugs, such as urethane, which have been put to new usage, are discussed.

Although no claim is made for this book as an investigator's handbook, still a fairly extensive and pertinent bibliography is included at the end of each section.

Because of its brevity (413 pages) and easy reading style, it would seem that this book would serve admirably as a "refresher" source for the busy practitioner and also as a text for medical students and nurses. CARL A. DRAGSTEDT.

IN a well organized and comprehensive monograph,[2] Karsner and Koletsky have presented the currently accepted teachings concerning the calcific changes which occur in the aortic valve.

By a selective use of the literature and with the addition of 200 of their own cases (only those with autopsies are included) they have arrived at their opinions. The statistical data have been analyzed properly and corrected for factors of error.

As would be expected, the stress is on the pathologic changes (macroscopic and microscopic). There are listed the morphologic alterations seen grossly and on histologic study. There is one chapter devoted to the clinical considerations, however.

Excellent photographs, photomicrographs, and tables are included.

There is a satisfactory concise historical review which actually indicates the reason for the publication.

They conclude that: (1) calcific disease of the aortic valve is largely the result of previous inflammation (principally rheumatic); (2) the entity is most common in white males of the older age groups; (3) enlargement (by weight) of the heart occurs in three-fourths of the cases; (4) the "electrocardiograms vary widely but are in accord with physical laws"; and (5) there is only a small factor of error in the x-ray diagnosis of calcification in the aortic region.

This volume is of major interest to internists and pathologists, is of value to any physician and surgeon, and should be readily available as a reference to all persons in the field of medicine.

M. C. WHEELOCK.

THE new *Textbook of the Nervous System*[3] by H. Chandler Elliott is designed for medical students and anyone beginning study of the human nervous system from a clinical standpoint. The author, realizing the student's necessity for knowing something about the nervous system before studying it in detail presents the story twice. The first 95 pages consist of an abbreviated description of the nervous system's form and function, with numerous simple diagrams for illustration, which incidentally throughout the book give the story in themselves. After such a "short cut" the entire nervous system is considered in the second part more completely and technically.

Here again the author does not use a conventional method of anatomical description but presents as far as possible a functional discussion of the parts of the nervous system in logical sequence, combining ana-

[1] ESSENTIALS OF PHARMACOLOGY. By Frances K. Oldham, M.Sc., Ph.D., F. E. Kelsey, Ph.D., and E. M. K. Geiling, Ph.D., M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

[2] CALCIFIC DISEASE OF THE AORTIC VALVE; A COMPREHENSIVE ANALYTIC SURVEY OF CALCIFIC SCLEROSIS. By Howard T. Korsner, M.D., and Simon Koletsky, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

[3] TEXTBOOK OF THE NERVOUS SYSTEM; A FOUNDATION FOR CLINICAL NEUROLOGY. By H. Chandler Elliott, M.A., Ph.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1947.

tomical description and analogies and diagrams to aid in the interpretation of the physiology.

The sequence of presentation is from the neuron and its parts through spinal cord and brain stem to the larger gray masses; the autonomic system being presented after consideration of the suprasegmental structures. Considerable space is properly given to functional systems in which there is clinical interest, as the auditory, vestibular, and gustatory systems and the visual system. A brief appendix lists the meanings of most neurological terms, and a working bibliography is included. An atlas of photographs of actual dissections and stained sections of brains completes the book.

The author's wish to avoid unnecessary anatomical detail has led to the illustrations possessing but few labels, and the structures he wishes to bring out are thus emphasized, as well as by the simplicity of design of many diagrams. A question might be raised as to whether or not there are enough labels and non-diagrammatic illustrations for the beginning student.

The style is lucid and at times pleasantly imaginative in the use of illustrative analogies. Because of his wish to have the student get a clear working knowledge of the basic brain one can sympathize with, if not entirely condone, the author's tendency to grasp firmly one horn of certain dilemmas, and be somewhat dogmatic in disputed areas. But references to recent literature are generously given in the text to give authority for statements and direct reading further. SAM L. CLARK.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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ESSAI DE PHYSIOPATHOLOGIE THYRO-HYPOPHYSAIRE; ETUDES CLINIQUES, THERAPEUTIQUES ET EXPERIMENTALES. By Jacques Mahaux. Paris: Masson & Cie, Editeurs; Liege: Editions Desoer, 1947.

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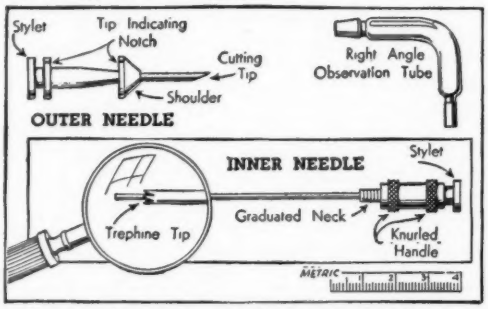

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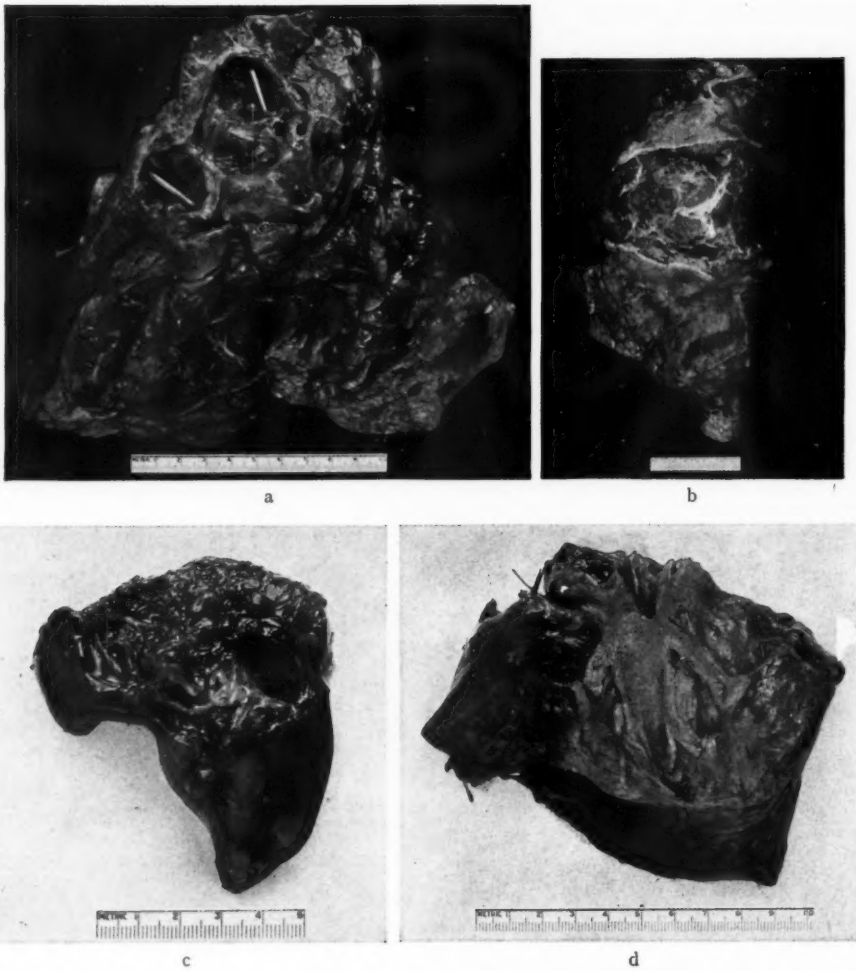

Fig. 5. a, Right lung removed at operation in case illustrated in Figure 4, a and b. Note the extensive destruction of lung tissue. b, Operative specimen of left upper lobe. Roentgenograms of this case are shown in Figure 6, a and b. c, Operative specimen of segmental resection of the superior division of the right lower lobe. This specimen is from the same case as shown in Figure 6, c and d. d, Right lower lobe which was removed for chronic lung abscess. The specimen reveals the presence of a small bone as the cause of abscess formation. See number 8 under "Indications for Pulmonary Resection."

Pulmonary Resection for Abscess of the Lung.—
Robert P. Glover and O. Theron Clagett